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**NUTRITION AS A MODIFIABLE RISK FACTOR FOR COGNITIVE DECLINE:
ASSOCIATED COGNITIVE AND PHYSICAL HEALTH CHANGES**

By

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A DISSERTATION

Submitted in Partial Fulfillment of the

Requirements for the Degree of

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(in Psychology)

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University of Maine

August 2023

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Dissertation Advisor: Fayeza S. Ahmed, Ph.D.

An Abstract of the Dissertation Presented
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Abstract

Dementia is defined as gradual, progressive loss of cognitive functioning, greater than what is expected of normal aging, resulting in functional impairment. There are several types of dementia clinical syndromes that are accompanied by unique patterns of cognitive dysfunction and neuropathological changes. Alzheimer's disease (AD) is the most common type of clinical dementia syndrome, accounting for approximately 60-70% of cases. Neuropathological mechanisms associated with AD include the disruption of the cholinergic system, accumulation of amyloid-beta plaques and hyperphosphorylated tau, as well as vascular pathology. Vascular pathology complicates the characterization of clinical and neuropathic changes in AD, as there becomes significant overlap with vascular dementia clinical presentation and pathology. Furthermore, many people with dementia have "mixed dementia," or brain changes associated with more than one cause of dementia. This may contribute to the difficulty establishing effective pharmacological interventions to reverse or prevent future neurodegeneration. As a result, research examining modifiable risk factors to prevent neuropathological changes associated with dementia, including AD, has become of interest. Modifiable risk factors include

physical activity, sleep, alcohol and tobacco use, and nutrition. Diet has been proposed to reduce risk of AD via neuroinflammatory mechanisms, oxidative stress, and by reducing risk for other comorbid medical conditions (e.g., vascular disease, diabetes, hypertension). There is limited research examining the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and cognition, longitudinally, in a middle-aged sample; furthermore, the potential moderating effect of APOE genotype, of which the e4 allele confers increased risk for AD. The current proposal provides a literature review of AD, including cognitive and neuropathological changes, as well as AD vascular factors and diet as a modifiable risk factor.

The proposed study aimed to examine the longitudinal effects of nonmodifiable risk factors (age, gender, APOE genetic status) and modifiable risk factors (MIND diet adherence and physical health) on cognition. In addition, to determine if APOE genetic status modifies the relationship between MIND diet and cognition, longitudinally. Participants included middle-aged adults with a family history of AD enrolled in the Wisconsin Register for Alzheimer's Prevention (WRAP) study. Latent Growth Curve (LGC) modeling was conducted to examine aims, assessing change across three visits (Visit 4 through Visit 6). Cognitive outcomes included previously established WRAP cognitive composite and factor scores. Upon examination of initial hypothesized models, empirical cognitive factor scores had significantly poorer model fit, and therefore, theoretically derived composite outcomes were used for structural modeling. Regarding physical health, waist-to-hip ratio (WHR) significantly reduced structural model fit across all theoretical cognitive outcomes, and therefore, WHR as a predictor of cognition was removed from analyses. Nonparametric correlations revealed, as expected, that WHR was negatively correlated with all cognitive outcomes (theoretical and empirical cognitive outcomes). Regarding diet, MIND diet adherence had unexpected significant negative effects on Theoretical

Executive Functioning (TEF) growth over time; however, APOE risk scores did not significantly moderate this relationship. Improving the understanding of causative relationships among underlying hypothesized mechanisms of dietary benefits on cognition and AD risk is crucial to reduce the burden of AD. The null findings highlighted important gaps in the literature that warrant additional investigation, including further examination of these relationships in cognitively and demographically diverse individuals and exploration of cognitive phenotypes associated with APOE risk.

DEDICATION

*To my parents,
Thank you for encouraging me to persevere when faced with challenges and in times of failure.*

*To my husband,
My rock, I couldn't have done this without your daily love,
support, and encouragement.*

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LIST OF ABBREVIATIONS

AA	Alzheimer's Association
A β	Amyloid-beta
A β ₄₂	Amyloid-beta 42
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
AD-C	Alzheimer's Disease with Clinically Observable Symptoms
AD-P	Alzheimer's Disease with Pathophysiological Process
ADAD	Autosomal Dominant Alzheimer's Disease
ADLs	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRC	Alzheimer's Disease Research Center
ADRDA	Alzheimer's Disease and Related Disorders
AHA	American Heart Association
AIC	Akaike Information Criterion
ALA	Alpha-linolenic Acid
APA	American Psychological Association
APP	Amyloid Precursor Protein
APOE	Apolipoprotein
APOE-e4	Apolipoprotein e-4 allele
ARIC-NCS	Atherosclerosis Risk in Communities Neurocognitive Study
ATP	Adenosine 5'-triphosphate
BBB	Blood Brain Barrier
BMI	Body Mass Index
BSLA	Baltimore Longitudinal Study on Aging
BVMT – R	Brief Visuospatial Memory Test – Revised
CBF	Cerebral Blood Flow
CES-D	Center for Epidemiologic Studies Depression Scale
CFI	Comparative Fit Index
CHAMPS	Community Healthy Activities Model Program for Seniors
CHAP	Chicago Health and Aging Project
CNS	Central Nervous System
Cook's <i>d</i>	Cook's Distance
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
CSF	Cerebrospinal Fluid
DASH	Dietary Approaches to Stop Hypertension
D^2	Mahalanobis Distance
DFA	Dietary Fatty Acid

DHA	Docosahexaenoic Acid
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DTI	Diffusion Tensor Imaging
E1	Error Term Variance 1
E2	Error Term Variance 2
E3	Error Term Variance 3
ESR	Empirical Story Recall
EHA	Eicosatetraenoic Acid
EO-FAD	Early-onset Alzheimer’s Disease
ESF	Empirical Speeded Flexibility
EIM	Empirical Immediate Memory
EVOO	Extra Virgin Olive Oil
FDG	Fluorodeoxyglucose
FFQ	Food Frequency Questionnaire
FLAIR	Fluid Attenuated Inversion Recovery
FTP	¹⁸ F-Flortaucipir
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HDL	High-density Lipoprotein
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
hs-CRP	High-sensitivity C-reactive Protein
IADLs	Instrumental Activities of Daily Living
ICC	Intraclass Correlation Coefficient
ICD	International Statistical Classification of Disease and Related Health Problem
IGF-1	Insulin-like Growth Factor, Type 1
IMean	Intercept Mean
KD	Ketogenic Diet
LA	Linoleic Acid
LGC	Latent Growth Curve
LGM	Latent Growth Modeling
LO-SAD	Late-onset Sporadic Alzheimer’s Disease
LDL	Low-density Lipoprotein
LRP1	Low-density Lipoprotein Receptor 1
M_{age}	Mean Age
MAP	Microtubule Associate Protein
MCI	Mild Cognitive Impairment
MD	Mediterranean Diet

MEGA ^{EX}	Expanded Multi-Ethnic Genotyping Array
MIND	Mediterranean-DASH diet Interventions for Neurological Delay
ML	Maximum Likelihood
MMSE	Mini-Mental State Examination
MOS	Medical Outcomes Study
MRI	Magnetic Resonance Imaging
MUFA	Monounsaturated Fatty Acid
NACC	National Alzheimer's Coordinating Center
nAChE	Nicotine Acetylcholinesterase
NCD	Noncommunicable Disease
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NO	Nitric Oxide
NVU	Neurovascular Unit
P-gp	P-glycoprotein
P-tau	Phosphorylated Tau
PASA	Posterior-Anterior Shift in Aging
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHF	Paired Helical Filaments
PLD3	Phospholipase D3
PNS	Peripheral Nervous System
PPA	Primary Progressive Aphasia
PS1	Presenilin 1
PS2	Presenilin 2
PUFAs	Polyunsaturated Fatty Acid
RAVLT	Rey Auditory Verbal Learning Test
RMSEA	Root Mean Square Error of Approximation
ROS	Reactive Oxygen Species
RNA	Ribonucleic Acid
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
SD	Standard Deviation
SEM	Structural Equation Modeling
SFA	Saturated Fatty Acid
SMean	Slope Mean
SRM	Standardized Response Means
STAC	Scaffolding Theory of Cognitive Aging
STAC-r	Scaffolding Theory of Cognitive Aging Revised
SUV	Standardized Uptake Values

SUVrs	Standardized Uptake Values Ratios
T-tau	Total Tau
TDM	Theoretical Delayed Memory
TEF	Theoretical Executive Functioning
TIM	Theoretical Immediate Memory
TF	Trans Fatty Acid
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TOL	Tolerance
TREM2	Triggering Receptor Expressed on Myeloid Cells 2
TLI	Tucker-Lewis Index
USDA	United States Department of Agriculture
V4	Visit 4
V5	Visit 5
V6	Visit 6
VaD	Vascular Dementia
VCID	Vascular Contributions to Cognitive Impairment and Dementia
VEGF	Vascular Endothelial Growth Factor
VIF	Variance Inflation Factor
WAIS-R	The Wechsler Adult Intelligence Scale – Revised
WD	Western Diet
WHO	World Health Organization
WMH	White Matter Hyperintensities
WMS-R	Wechsler Memory Scale – Revised
WRAP	Wisconsin Registry for Alzheimer’s Prevention
χ^2	Chi-Square

CHAPTER 1

INTRODUCTION

Worldwide, an estimated 50 million people currently have dementia with an incidence rate of 10 million each year (World Health Organization [WHO], 2020). These rates are expected to continue increasing, reaching approximately 82 million people worldwide by 2030 (WHO, 2020). Aging is associated with overall gradual degeneration of body structure and function (Wagner et al., 2016). The brain undergoes unique changes associated with the aging process which include progressive neuronal loss and cognitive decline (c.f. Yankner et al., 2008). Often, cognitive decline is further accompanied by oxidative damage, neuroinflammation, accumulation of protein aggregates, along with loss of myelin, neurons, and synapses (Cole et al., 2010); however, all these changes can be a normal part of the aging process. Dementia is characterized by cognitive decline that extends beyond normal aging (WHO, 2020).

Severity and extent of cognitive impairment can vary depending on etiology or type of dementia clinical syndrome. Ultimately, there is no established cure for dementia and neurodegeneration eventually becomes fatal. As a result, researchers have attempted to develop pharmacological interventions; however, treatment outcomes are poor (Elmaleh et al., 2019). Attempting to understand what elements put individuals at risk for dementia, researchers have examined several different factors including, but not limited to, age, family history, and genetic susceptibility (Alzheimer's Association [AA], 2019). There remain limitations associated with the aforementioned risk factors, as they are unchangeable. Given that pharmacologic interventions remain unsuccessful, there is growing interest in examining modifiable risk factors (WHO, 2019). Modifiable risk factors are malleable. Lifestyle changes can be feasibly implemented and mitigate risk, either preventing or delaying the onset of disease. Modifiable

risk factors that correspond with dementia risk include physical inactivity, tobacco and problematic alcohol use, poor sleep, unhealthy diet adherence (WHO, 2019), cognitive inactivity, and obesity (Barnes & Yaffe, 2011). Importantly, the aforementioned lifestyle factors contribute to the development of other health conditions, like diabetes, mid- and late-life hypertension, hypercholesterolemia, and obesity (WHO, 2019), all of which increase the risk for developing dementia later in life. In summary, the modification of dementia risk can potentially occur through various mechanisms, but they primarily reduce negative consequences of physical inactivity, substance use, poor sleep, and unhealthy diet on brain and physical health.

In this dissertation, I will first define all-cause dementia and Alzheimer's disease (AD), including clinical characteristics. Next, I will provide a review of hypothesized neuropathological changes associated with AD, followed by literature communicating the importance of considering vascular health in AD neuropathology and briefly compare AD to vascular dementia (VaD). Subsequent sections will present the existing literature discussing the impact of unchangeable risk factors (e.g., age, sex, race, and genetics) and diet (modifiable risk factor) on AD risk. Of all the risk factors introduced, the current dissertation will focus on the influence of diet and nutrition on cognition and physical health characteristics. Therefore, a full chapter will be dedicated to discussing the mechanisms to which diet and nutrition may reduce risk for dementia and AD before the aims are introduced. Lastly, the dissertation will summarize the results of the current study and important conclusions, including limitations and future directions.

CHAPTER 2

DEMENTIA, ALZHEIMER'S DISEASE AND ASSOCIATED NEUROPATHOLOGY

2.1 Defining Dementia

Dementia is defined as gradual, progressive loss of cognitive function (Kukull & Bowen, 2002), greater than what is expected with normal aging (WHO, 2020) resulting in functional impairment. Depending on the type of dementia syndrome, several cognitive domains can be affected which include, but are not limited to, memory, comprehension, executive functioning, judgment, language, learning (WHO, 2019), visual spatial abilities, processing speed, and/or attention. Importantly, the neurodegenerative process is also associated with behavioral changes (e.g., agitation, depression, apathy, irritability, etc.) (Kukull & Bowen, 2002), and functional changes (e.g., quality of life, activities of daily living (ADLs), and instrumental ADLs (IADLS); WHO, 2019).

The Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5; American Psychological Association [APA], 2013), has common criteria used for the clinical diagnosis of dementia and other neurocognitive disorders. According to the DSM-5, a major neurocognitive disorder is characterized by significant cognitive decline from previous abilities in one or more cognitive domains, including complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition (APA, 2013). This cognitive decline is based on concern from the individual, a knowledgeable informant, and/or a clinician. Additionally, impairment in cognitive performance must be substantial and preferably documented by standardized neuropsychological testing, or in its absence, another clinical

assessment that characterizes decline (APA, 2013). The established cognitive deficits must interfere with everyday activities, and minimally interfere with IADLs (e.g., managing finances, remembering appointments, medication management, etc.). To be characterized as a neurocognitive disorder, the cognitive decline cannot be exclusive to a state of delirium and is not better explained by another mental disorder (APA, 2013). If possible, the suspected etiology should accompany the diagnosis and can include the following: Alzheimer's disease (AD), frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, or unspecified (APA, 2013). Notably, there are other causes of dementia that should be considered, such as vitamin B12 deficiency, hypothyroidism, and stroke (Kukull & Bowen, 2002). Within each etiological subtype, the diagnosis can indicate possible or probable dementia, depending on the core features, presence of neuropathology, historical data, genetic testing, and/or other clinical features (Kukull & Bowen, 2002). Other specifiers include with or without behavioral disturbance and severity (i.e., mild, moderate, or severe) (APA, 2013).

The DSM-5 criteria follow criteria outlined by the National Institute on Aging and the Alzheimer's Association workgroup, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders (ADRDA). The NINCDS-ADRDA first developed a core criteria for the diagnosis of AD dementia in 1984 (McKhann et al., 1984). The 1984 clinical criteria were revised in 2011 due to the further understanding of clinical manifestation and biology (McKhann et al., 2011). However, to understand the clinical diagnostic criteria for AD, it is important to understand the changes that occur in all-cause dementia, or neurological changes that are not specific to dementia syndromes

(i.e., AD, vascular dementia, etc.). Overall, the criteria for major neurocognitive disorder, according to the DSM-5, are relatively similar to the NINDS-ADRDA criteria for all-cause dementia. According to the NINDS-ADRDA criteria, all-cause dementia is defined as cognitive or behavioral (neuropsychiatric) symptoms that interfere with the ability to function at work or during usual activities, represent a decline from previous functioning and performance levels, and are not explained by delirium or major psychiatric disorder (McKhann et al., 2011).

Furthermore, the NINDS-ADRDA criteria indicate that cognitive impairment is detected and diagnosed through a combination of the following: (1) history-taking from the patient and knowledgeable informant, as accurate descriptions of presenting concerns can be limited with the onset of dementia and/or neurodegeneration; (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing (neuropsychological testing should be performed when the routine history and bedside mental status examination cannot be confident in the diagnosis); (3) the cognitive or behavioral impairment involves minimally, two cognitive domains (McKhann et al., 2011). Cognitive domains that can be affected include impaired reasoning and handling of complex tasks, learning, visuospatial abilities, language functions, and/or changes in personality, behavior, or comporment (McKhann et al., 2011).

2.2 Alzheimer’s Disease

Alzheimer’s disease is the most common type of clinical dementia syndrome, accounting for 60-70% of cases (WHO, 2019). It is marked by loss of neuronal structure and function (Przedborski et al., 2003). No pharmacological interventions developed for AD successfully slow or prevent future neuronal destruction (AA, 2019). As mentioned previously, the DSM-5 is one clinical diagnostic tool for the diagnosis of major neurocognitive disorder, or all-cause dementia, and specific dementia syndromes, including AD. Another diagnostic tool commonly used in

medical settings, and used in conjunction with the DSM-5, is the International Statistical Classification of Disease and Related Health Problem (ICD) codes, which are medical classification codes provided by the WHO. Additionally, the NINCDS and ADRDA workgroups have developed specific core criteria for the diagnosis of AD dementia in 1984 (McKhann et al., 1984). As mentioned previously, the 1984 clinical criteria were revised in 2011 due to further understanding of clinical manifestation and biology to improve specificity in determining probable or possible AD (McKhann et al., 2011).

Probable AD dementia is diagnosed when an individual meets criteria for all-cause dementia (as defined by the NINDS-ADRDA) and additionally displays the following characteristics: (1) insidious and gradual symptom onset, a period over months to years; (2) a clear-cut history of worsening cognition by report or observation; and (3) the initial and prominent cognitive deficits are evident on history and examination, consistent with either amnesic or nonamnesic presentations (McKhann et al., 2011). Amnesic is the most common presentation for AD dementia and is characterized by deficits in learning and information recall (McKhann et al., 2011). Often, individuals display cognitive dysfunction in at least one other domain in addition to learning and memory (McKhann et al., 2011). In contrast to the amnesic presentation, nonamnesic presentations can include deficits in language, visuospatial, and/or executive functioning (McKhann et al., 2011). Of note, the diagnosis of probable dementia should not be applied if there is evidence of cerebrovascular disease, core features of dementia with Lewy bodies, prominent features of behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia (PPA) or nonfluent agrammatic variant PPA, or evidence for another concurrent neurological or non-neurological comorbidity that may significantly impact cognition (McKhann et al., 2011).

In addition to the core clinical features of probable AD, there are other aspects that can increase the level of diagnostic certainty. First, well documented cognitive decline iterates the pathologic process is evolving and active. Second, there are several genetic mutations, including amyloid precursor protein (APP), presenilin-1 (PS1), or presenilin-2 (PS2), of which are linked to AD pathology. Possessing one of the established genetic mutations increases certainty of AD etiology (McKhann et al., 2011).

In contrast to probable AD, possible AD conveys slightly less certainty in establishing AD as the underlying pathological process. A diagnosis of possible AD dementia should not be provided if the onset of cognitive decline is atypical (McKhann et al., 2011). Although individuals may meet the core clinical criteria and present with cognitive deficits that may be consistent with what is expected for AD dementia, possible AD should not be diagnosed if the course of impairment is rather sudden, or there is not enough historical data and/or objective cognitive data to document the progressive decline (McKhann et al., 2011). Alternatively, a diagnosis of possible AD dementia can be provided if the individual appears to have a mixed etiological presentation. An etiologically mixed presentation has evidence for co-occurring cerebrovascular disease, or features of dementia with Lewy Bodies, or there is evidence for another neurological or non-neurological medical comorbidity, such as medication use, that could have an impact on cognition (McKhann et al., 2011).

Unlike probable and possible AD, definite AD can only be confirmed by autopsy. Even so, in individuals that meet the core criteria for probable AD, additional biomarker evidence for pathophysiological changes can further increase the level of certainty during clinical diagnosis that AD is the basis of the clinical dementia syndrome (McKhann et al., 2011). AD biomarkers will be discussed in greater detail in the *Neuropathology of AD* section, but briefly, examining

AD-related biomarkers may first include assessment of brain amyloid-beta deposition, as measured by $A\beta_{42}$ in cerebrospinal fluid (CSF) and/or evidence of amyloid-beta plaques found on positron emission tomography (PET) amyloid imaging (Chetelat et al., 2010; Jack et al., 2008). Next, biomarkers of downstream neuronal degeneration or injury are assessed (McKhann et al., 2011). These include CSF tau (total (t-tau) and phosphorylated tau (p-tau)), decreased 18 fluorodeoxyglucose (FDG) uptake on PET imaging in the temporo-parietal cortex, and significant atrophy on structural magnetic resonance imaging (MRI) in the medial, basal, and lateral temporal lobes, and in the medial parietal cortex.

Overall, the clinical criteria created by the NINDS-ADRDA, DSM-5, and ICD provide guidance when diagnosing the clinical presentation of AD. Notably, it is possible to see evidence for the AD pathophysiological process (AD-P) without clinically observable syndromes (AD-C) (Jack et al., 2011). The following section will discuss the AD pathological changes in further detail.

2.2.1 Neuropathology of Alzheimer's Disease

The previous section summarized the clinical presentation of AD (AD-C) (Jack et al., 2011), however, there are several neuropathological changes that occur in AD. The AT(N) classification system was first proposed in 2016 by Jack and colleagues (Jack et al., 2016). It is a conceptual framework for characterizing neuropathological changes that occur in AD (amyloid-beta aggregation (A), tau-mediated pathophysiology (T), and neuronal injury/neurodegeneration (N)), as measured by biomarkers. Recently, the AT(N) framework was expanded to include a new array of biomarkers (X). The goal was to create a placeholder for novel and newly researched biomarkers that capture the molecular and cellular changes that occur in the brain, resulting in alterations in neuroimmune and neuroinflammatory systems, as well as

microvascular pathology and synaptic dysfunction (Hampel et al., 2021). Existing research, which will be discussed in upcoming sections, suggests that risk factors associated with neurodegeneration (neuroinflammation, oxidative stress, vascular health, and the effectiveness/abundance of neuroprotective mechanisms) and with 'X' in the ATX(N) framework, can begin to change as early as midlife (Sperling et al., 2011). Many of these hypothesized mechanisms have not only been associated with modifiable risk factors, such as nutrition, but are also associated with vascular health changes. These early changes in brain are likely occurring decades before the onset of AD symptoms (Sperling et al., 2011).

Neuropathological changes, including disruption in the cholinergic system, accumulation of amyloid-beta plaques and hyperphosphorylated tau, and vascular pathology, will be discussed in the following section.

2.2.1.1 Alzheimer's Disease and the Cholinergic System

Acetylcholine is a neurotransmitter that is used by cholinergic neurons, which are widely distributed in the peripheral (PNS) and central nervous system (CNS) (Armstrong et al., 1983; Woolf & Butcher, 2011). In fact, nearly all regions of the brain are innervated by cholinergic neurons (Armstrong et al., 1983). In AD, cholinergic neurons degenerate contributing to AD-related memory loss (Whitehouse et al., 1981; Whitehouse et al., 1982). With cholinergic neuron degeneration, deficits in cholinergic transmission are also seen in AD resulting in cognitive and behavioral consequences (Bartus, 2000). Cholinergic synapses are negatively affected in AD once the brain begins to show early signs of amyloid-beta neurotoxicity (Bell et al., 2006; Wong et al., 1999). Clinically, the synaptic loss results in cognitive impairments (Selkoe, 2002; Terry et al., 1991).

There is an overall lack of cholinergic innervation seen in early AD, especially in the cortex and hippocampus (Karran et al., 2011; Nilsson et al., 2011). As summarized by Lukiw (2012), pharmacological interventions targeting inhibition of acetylcholinesterase (AChE) are one of the most common treatments for mild to moderate AD. Mechanistically, AChE inhibitors target brain regions that are commonly depleted of acetylcholine in AD by increasing acetylcholine concentration levels and supporting neurotransmission. When examining the pharmacological interventions more closely, most interventions increase activity of nicotine acetylcholine receptors (nAChRs) (Karran et al., 2011; Nilsson et al., 2011). These receptors are suspected to protect the brain against neurotoxicity associated with glutamate and amyloid-beta, and also enhance learning and memory (Akaike & Izumi, 2018).

2.2.1.2 Amyloid Cascade Hypothesis

In both probable and possible AD dementia, the evidence of pathophysiological changes associated with an AD process can increase the level of certainty in diagnosis (McKhann et al., 2011). The Amyloid Cascade Hypothesis (Figure 1) was one of the first proposed hypotheses that characterized pathological changes associated with AD. It has dominated the field of AD research for decades and accelerated the examination of therapeutic modalities (Karran et al., 2011).

According to the Amyloid Cascade Hypothesis, there are two pathological changes that occur in the brain and both can only be definitively confirmed via autopsy (McKhann et al., 1984). As summarized by Schoenberg & Duff (2011), these changes are suspected to begin in the medial temporal lobes (entorhinal cortex and hippocampi), spreading to the parietal and frontal cortices, and eventually consuming majority of the neocortex. First, there is excessive accumulation of amyloid-beta peptides outside of the cells leading to the creation of amyloid-

beta plaques (Bloom, 2014), which disrupts and interferes with synaptic communication between neurons, ultimately triggering neuronal dysfunction (AA, 2019), neurotoxicity due to excessive accumulation of $A\beta_{42}$, and neurodegeneration (Hensley et al., 1994). In addition to amyloid-beta plaques in AD, tau proteins accumulate inside the neuron. The tau proteins become misfolded and abnormally shaped, creating hyperphosphorylated tau-tangles that prevent nutrient and essential molecule transportation. Ultimately, the tangles disrupt the cell's integrity leading to cell death (AA, 2019). Overall, it is thought that excessive accumulation of these two proteins yields change in cognitive functioning, traditionally affecting memory first and then progressing to other domains (e.g., language, reasoning, etc.) (Saykin & Rabin, 2014).

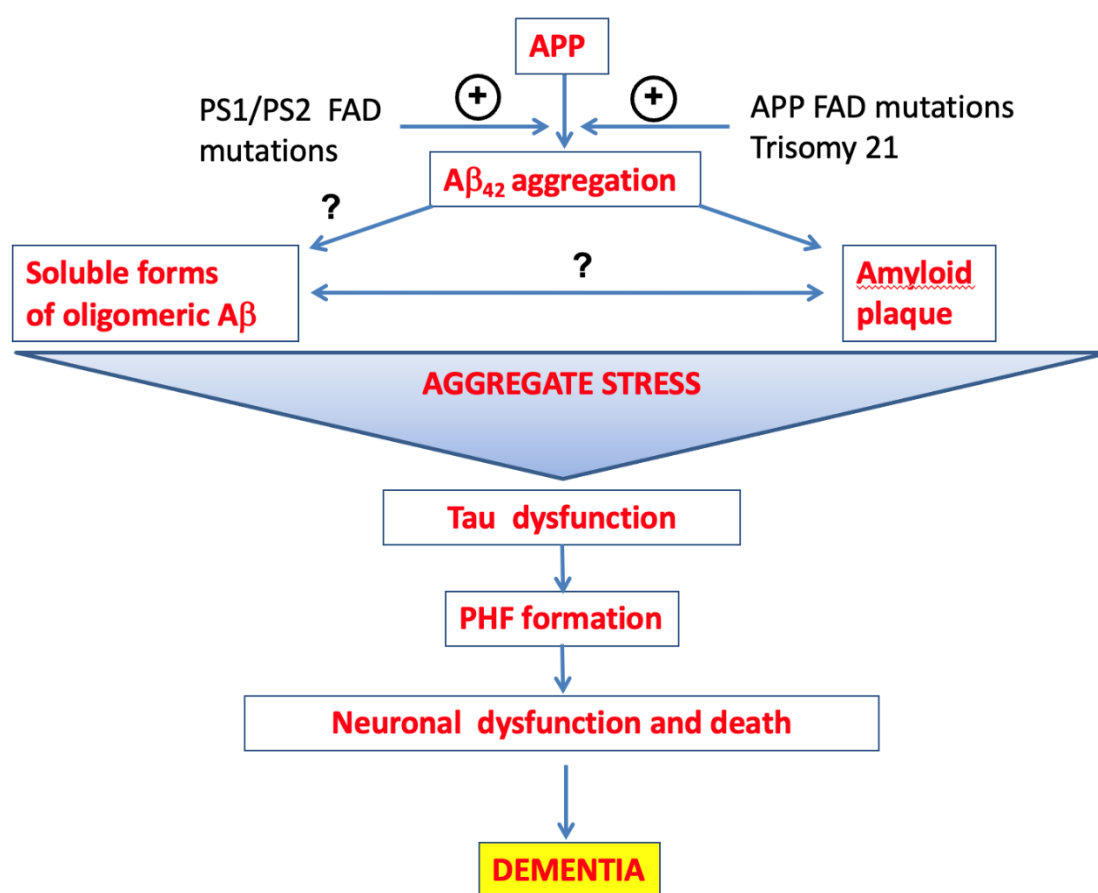
As mentioned previously, the accumulation of amyloid-beta plaques is one of the first neuropathological changes thought to occur in AD. Amyloid-beta peptides are derived from a larger precursor protein, APP (Chen et al., 2017). APP is a membrane protein that is expressed in many tissues, including neurons. They are particularly important for synaptic formation and repair (Priller et al., 2006), anterograde neuronal transport (i.e., moving cells outward from the soma to the synapse or cell membrane) (Turner et al., 2003), and iron export (Duce et al., 2010). To produce amyloid-beta and other peptides, the precursor molecule APP is cut into amino acid residue peptides (Nunan & Small, 2000).

Amyloid-beta is considered a monomer and can bind with similar molecules to create a polymer (Chen et al., 2017). Continued binding outside of the cell leads to aggregates, which can assemble into oligomer, protofibrils, and amyloid fibrils. Amyloid fibrils, in particular, can continue to assemble, causing amyloid plaques (Chen et al., 2017). According to the Amyloid Cascade Hypothesis, the amyloid-beta fibrils ultimately act as a neurotoxic agent resulting in cell death and memory loss, among other AD associated changes (Chen et al., 2017). Furthermore,

amyloid-beta oligomers may induce mitochondrial dysfunction and oxidative stress in AD, which can also result in toxicity (Canevari et al., 2004). Some receptors continue to bind with amyloid-beta, whereas other receptors assist in clearance (Chen et al., 2017). For example, microglial receptors bind with amyloid-beta, but assist in clearance; however, microglial activation can trigger a neuroinflammatory response (Chen et al., 2017).

Figure 1

Amyloid Cascade Hypothesis



Note. Figure from Karran et al. (2011). Aβ₄₂ = amyloid-beta 42; APP = amyloid precursor protein; PS-1 = presenilin 1; PS-2 = presenilin 2; FAD = early onset familial Alzheimer's disease; PHF = paired helical filaments (tau aggregates).

Additional research has examined the genetic basis for AD and how it changes associated AD neuropathology. Early-onset familial Alzheimer's disease (EO-FAD) is marked by disease onset before age 65 and is less common, accounting for less than 5% of AD (Tanzi, 2012). EO-FAD is an autosomal-dominant disorder and has one of the following genetic mutations: APP, PS1, PS2 (Tanzi, 2012). Late onset sporadic Alzheimer's disease (LO-SAD), or late-onset Alzheimer's disease (LOAD), represents most cases of AD. It is hypothesized that LO-SAD is influenced by multiple factors, including genetic susceptibility and environmental risk (Lambert & Amouyel, 2011). There are no established genetic mutations in LO-SAD, however, there are several major genetic risk factors, including the APOE-e4 allele (Corder et al., 1993; Strittmatter, Saunders, et al., 1993). Research indicates the neuropathological and clinical changes are quite similar in EO-FAD compared to LO-SAD; however, there may be important differences to consider. Specifically, some research suggests that APP mutations in EO-FAD are associated with poor amyloid-beta clearance that may mediate aggregation and clearance (Kowalska, 2003). Additionally, in LO-SAD, it has been hypothesized APOE-e4 status may modulate amyloid-beta aggregation and clearance (Bu, 2009), both enhancing deposition and reducing clearance (Bales et al., 1999; Holtzman, 2001; Holtzman et al., 2000; Shibata et al., 2000; Strittmatter, Weisgraber, et al., 1993).

Tau is a microtubule associated protein (MAP) normally detected within the CNS (Ameri et al., 2020). It is important for the stabilization and polymerization of microtubules (Weingarten et al., 1975) and facilitating axonal transportation (Ghetti et al., 2015; Mandelkow & Mandelkow, 2012). Phosphorylation of tau is a naturally occurring process and critical for microtubule regulation (Ameri et al., 2020). In AD, there is a significant increase in the average number of phosphate groups per tau molecule and the protein detaches from the microtubule

(Kanemaru et al., 1992; Kopke et al., 1993), resulting in hyperphosphorylation.

Hyperphosphorylated tau molecules can contribute to synaptic malfunction, modify degradation, increase aggregation, and alter molecule interactions (Wang & Mandelkow, 2016). Additionally, hyperphosphorylated tau significantly contributes to neurofibrillary tangles commonly observed in AD (Rajmohan & Reddy, 2017). As mentioned previously, tau proteins become misfolded and abnormally shaped in AD, creating tangles that prevent nutrient and essential molecule transportation. Ultimately, the tangles disrupt the cell's integrity (AA, 2019), leading to disruption in neuronal communication and signal processing (Lee et al., 2001).

2.2.1.2.1 Biomarkers

A biomarker, also known as biological marker, is a measurable and objectifiable biological substance found in the body that provides information about an individual's biological and pathogenic processes, along with pharmacological responses to therapeutic interventions (Biomarkers Definitions Working, 2001). Biomarkers for amyloid-beta and tau have been widely examined for better detection of AD (McKhann et al., 2011). There are two identified biomarkers to capture the presence of amyloid-beta protein deposition. First, the level of $A\beta_{42}$ in CSF can be examined (McKhann et al., 2011). Amyloid-beta (Iliff et al., 2012), extracellular tau (Patel et al., 2019) and lactate (Lundgaard et al., 2017) are all removed via the glymphatic pathway, a highly sophisticated fluid transport system that clears waste metabolites (Hauglund et al., 2020). Therefore, low levels of $A\beta_{42}$ in the CSF are an important AD biomarker (Jack et al., 2008), as it may be indicative of reduced waste removal (i.e., amyloid-beta) via the glymphatic system washout and greater amyloid-beta aggregation. In addition to $A\beta_{42}$, CSF can measure other amyloid-beta species. In fact, $A\beta_{1-40}$ are more prevalent, with 10 times higher concentration levels in CSF compared to $A\beta_{42}$ (Portelius et al., 2007; Portelius et al., 2006). Compared to $A\beta_{42}$

alone, some studies suggest that measuring the ratio of $A\beta_{42}/A\beta_{40}$ may be a better indicator of AD pathology and show greater concordance with amyloid positivity shown on PET imaging (Janelidze et al., 2016; Lewczuk et al., 2017; Pannee et al., 2016).

In addition to CSF, amyloid-PET and FDG PET imaging (2-Deoxy-2-[^{18}F] fluorodeoxyglucose ([^{18}F] FDG PET)) can provide information regarding amyloid accumulation (Grothe et al., 2017) and can improve accuracy of AD diagnoses. FDG PET utilizes cutoff points for glucose standardized uptake values (SUVs). In AD diagnosis, uptake intensity is normalized and compared to the mean metabolic rate for the whole brain or cerebral glucose consumption. Therefore, brain areas that have greater amyloid burden have poorer glucose uptake (Dukart et al., 2010). Research suggests that AD pathology also leads to hypometabolism, in other words reduced glucose uptake, on PET in the temporo-parietal cortex (McKhann et al., 2011). Including FDG PET in the clinical assessment for AD can increase diagnostic certainty, however, it should not be used in solitude as it has some limitations. More specifically, scan interpretation accuracy declines significantly in older patients. Sensitivity studies suggest FDG PET has 100% sensitivity, 75% specificity, and 84% accuracy rate in a middle-aged cohort, ($M_{\text{age}} = 64$ years). When compared to older patients, FDG PET has 20% lower accuracy, specifically in LO-SAD (the most common type of AD) (Ng et al., 2007). Reduced sensitivity, specificity, and accuracy in older patients could partially be due to the increased anatomical overlap that is sometimes associated with age (Rabinovici et al., 2007; Womack et al., 2011). For example, distinguishing between temporoparietal predominant AD versus anterior temporal regions in frontotemporal lobar degeneration (a specific dementia syndrome) is more difficult with anatomical overlap (Foster et al., 2007; Rabinovici et al., 2007). In other words, as patients get older, brain structures that are affected by neurodegeneration and/or a dementia syndrome

become less distinct which creates difficulty in ruling out differential diagnoses. Overall, research suggests that CSF A β ₄₂ and amyloid PET imaging may be used interchangeably in a clinical setting, depending on availability and cost. Both have unique benefits for assisting in AD diagnosis, but both should be considered carefully.

T-tau and p-tau can be observed in CSF and is another suggested method for early detection of AD (Li et al., 2016). In general, elevated levels of tau protein in CSF are indicative of neurodegeneration and axon damage (Lee et al., 2019). For AD more specifically, both CSF t-tau and p-tau may be indicative of an AD process (Bjerke & Engelborghs, 2018; Shui et al., 2018). In fact, higher CSF t-tau and p-tau predict more rapid disease progression (Buchhave et al., 2012; Hansson et al., 2018; Hertze et al., 2010; Wallin et al., 2010). Although there are elevated levels of CSF t-tau in AD, t-tau only provides a marker for neuronal injury and/or neurodegeneration (Blennow & Hampel, 2003), which is present in other neurological disorders, and should not be used in solidarity. On the other hand, p-tau is considered more related to AD due to associated neuropathological changes.

2.2.1.2.2 Problems with the Amyloid Cascade Hypothesis

As mentioned previously, the Amyloid Cascade Hypothesis dominated the field of AD research for decades. Early studies established a strong link between amyloid plaques and AD, and the hypothesis offered a broad framework for understanding the role of amyloid-beta in AD pathology (Hardy & Selkoe, 2002). With additional research, however, it became clear AD pathology is much more complex than what was originally proposed by the Amyloid Cascade Hypothesis. In fact, many argue the Amyloid Cascade Hypothesis lacks detail, and the observations of later studies are not consistent with the hypothesis (Hardy & Selkoe, 2002). Following the hypothesis proposal, studies began to demonstrate no correlation between the

presence of amyloid-beta plaques and synaptic and neuronal loss in AD (Masliah et al., 1992; Masliah et al., 1991). More recent studies suggest it is the combination of amyloid-beta neurotoxicity and tau that mediate neuronal cell loss (Jeong, 2017), and also partially due to mitochondrial dysfunction (Knott et al., 2008; Sunram-Lea & Owen, 2017). Additionally, the number of amyloid deposits does not correlate with the degree of cognitive impairment. This finding is demonstrated in pharmacological treatment studies, which indicate that even with the reduction of amyloid-beta depositions via pharmacological intervention after the onset of AD, treatments have failed to show clinical benefits in phase III clinical trials (Vaz & Silvestre, 2020). Furthermore, tau pathology (Chetelat, 2013) and amyloid-beta plaque accumulation, independently, are not exclusive to AD and are only weakly correlated with pathology severity, as summarized by Chen et al. (2017).

Overall, there is some research questioning the causal role of amyloid-beta in AD. Originally, as proposed by the Amyloid Cascade Hypothesis, amyloid-beta depositions contributed to AD. However, additional research suggests APP and other metabolites, including amyloid-beta protein, are important for regulating neuronal functions such as cell excitability, synaptic transmission, and neural plasticity (Nguyen, 2015). In other words, APP and amyloid-beta protein, to some extent, are important for maintaining brain health, which suggests AD is more complex than the initial and hypothesized causal insult of amyloid-beta deposition (Chetelat, 2013; Nguyen, 2018).

With additional research, the unitary view that AD is a single sequential pathology is diminishing. The hypothesis fails to consider how tau and amyloid-beta depositions interact with each other in AD neuropathology (Karran et al., 2011). Given that the presence of tau tangles and amyloid-beta plaques can occur independently, outside the pathological changes associated

with AD, it is likely they both have their own independent risk factors (Chetelat, 2013).

Therefore, it is unclear about whether amyloid-beta plaques are an initial causal event to AD or are a result AD pathophysiological changes.

The Amyloid Cascade Hypothesis was one of the first hypotheses that attempted to characterize neuropathological changes occurring in AD. It encouraged research to identify treatments targeting neuropathological changes; however, treatment outcomes have been poor. Additional research examining the Amyloid Cascade Hypothesis also revealed limitations to the hypothesis, including failure to capture vascular changes and associated pathology which also occur in AD. Vascular risk and associated neuropathological changes will be the focus of the following sections. Before AD-specific vascular pathology is discussed, the neurovascular unit (NVU) will be introduced to provide context for understanding cerebrovascular health.

2.3 The Neurovascular Unit

Aging is associated with cell damage throughout the human body, which subsequently impairs cells' functional abilities and structural components. In the brain, neurons transmit signals facilitating communication across neurons. Healthy and efficient brain functioning depends on neuron communication, along with the integrity of the specific NVU components (Cai et al., 2017). The NVU first emerged from the original Stroke Progress Review Group meeting of the National Institute of Neurological Disorders and Stroke of the National Institute of Health (July 2001) to characterize the relationship between neuronal cells and cerebral vasculature (<https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/Stroke-Progress-Review-Group>). The NVU is a multicomponent unit facilitating healthy brain function and helps maintain the brain's structural integrity (Li et al., 2019). Unit components include neurons, glial cells (oligodendrocytes, microglia, and astrocytes), vascular

cells (pericytes, endothelial cells, and smooth muscle cells), and the basal lamina matrix (Cai et al., 2017; Harder et al., 2002; Lecrux & Hamel, 2011; Lo & Rosenberg, 2009).

Each component of the NVU is closely linked and relationships among the components are reciprocal (Fields & Stevens-Graham, 2002; Simard et al., 2003). Neurons are often labeled the pacemakers of the NVU (Banerjee & Bhat, 2007; Koehler et al., 2006). They are quick to detect subtle changes in nutrient and oxygen supply in the brain. Once the changes are detected, neurons signal other interneurons and astrocytes via electrical or chemical signals (Figley & Stroman, 2011).

Arguably, one of the most important components of the NVU are glial cells which surround the neuron, prevent neurons from having direct contact with vascular cells, as the molecules within neurons and vascular cells are different (Gelfand et al., 2009), and protect against blood-borne substances that may be harmful to the cell (Cai et al., 2017).

Oligodendrocytes, microglia, and astrocytes are all specific types of glial cells. Oligodendrocytes produce lipid-enriched myelin that wrap the axons to accelerate conduction of an action potential (McTigue & Tripathi, 2008). Microglia are well-known for their ability to recognize pathogens and consume foreign bodies that may be harmful (Amor et al., 2010; Wake et al., 2011). They are also called the “garbage trucks of the brain” and are known as the first line of defense in the CNS, protecting the brain from external insults by regulating synaptic plasticity, repairing neuronal circuits, and maintaining homeostasis in the brain (Van Eldik et al., 2016). Lastly, astrocytes bridge the communication between glial cells and other neurons among specialized networks (Cornell-Bell et al., 1990; Muoio et al., 2014), and are often conceptualized as the NVU links (Abbott et al., 2006). They regulate CBF, by monitoring neuronal activity and contributing to neurovascular coupling (Cai et al., 2017) and capillary permeability (Abbott et

al., 2006). Astrocytes also provide structural and nutritional support for neurons (Van Eldik et al., 2016), and detect glutamate and GABAergic levels (Duchemin et al., 2012; Pelligrino et al., 2011; Zonta et al., 2003). Additionally, astrocytes produce and release several different substances that may be important for dilation and constriction of blood vessel walls (i.e., vasodilation and vasoconstriction), such as adenosine triphosphate (ATP), prostaglandins, and nitric oxide (NO) (Gordon et al., 2008).

In addition to glial cells, the NVU also contains vascular cells including pericytes, endothelial cells, and smooth muscle cells. Pericytes are in close contact with endothelial cells (Muoio et al., 2014). Structurally, pericytes provide support to endothelial cells during development and maturation periods. Possibly their most fundamental role, however, pericytes contribute to blood-brain barrier (BBB) development and integrity (Armulik et al., 2010; Daneman et al., 2010), phagocytosis, and the development of new blood vessels (Armulik et al., 2010). As summarized by Muoio et al. (2014), endothelial cells produce a variety of substances that contribute to the overall function of the NVU. Endothelial cells surround brain capillaries, forming a tube-like structure (Zlokovic, 2011). In turn, endothelial tubes are surrounded by pericytes, astrocyte end-feet, and the extracellular matrix which forms the basement membrane (Yu et al., 2020; Zlokovic, 2011). Together, endothelial cells, pericytes, and astrocytes form inter-endothelial tight junctions (TJ) (Bonkowski et al., 2011; Jo et al., 2013), which act as CNS gatekeepers (Luissint et al., 2012) and limit paracellular permeability of the BBB (Zlokovic, 2008). TJs prevent free diffusion of proteins and seal the paracellular cleft between endothelial cells (Tietz & Engelhardt, 2015). In other words, TJs limit permeability and maintain integrity of the BBB.

In summary, the BBB is controlled by pericytes and embedded in the basement membrane, microglial cells, astrocytes, and neurons. Together, these constitute the NVU and support BBB functioning. The primary purpose of the BBB is regulating which cells and/or molecules enter the brain and clear out harmful proteins (Yamazaki & Kanekiyo, 2017). The various components of the NVU work together, protecting the brain and maintaining brain homeostasis (Muioio et al., 2014). If the NVU is disrupted, a series of cascading consequences involving reduced CBF, BBB disruption (Iadecola, 2010, 2013; Sagare et al., 2012; Stanimirovic & Friedman, 2012; Zlokovic, 2005), neuronal cell death, glial cell reaction, and immune cell infiltration (Sohrabji et al., 2013) can occur. Once disruption occurs in the NVU, it becomes a negative cycle inducing further damaging responses such as inflammation, oxidative stress, and upregulation of vasoconstrictors (Iadecola, 2013; Lyros et al., 2014; Montagne et al., 2015). In fact, vascular oxidative stress and inflammation are two suspected factors contributing to neurovascular dysfunction. Oxidative stress is defined as an imbalance between oxidants and antioxidants (Huang et al., 2016), which can result in accumulated DNA damage and impairment in DNA repair process (Li et al., 2019). This compromises the genetic integrity of neurons and other cells within the NVU (Li et al., 2019) and excessive accumulation of DNA damage can contribute to the neurodegenerative process (Choi et al., 2012; Hou et al., 2018; Suberbielle et al., 2015). Notably, neurons are highly susceptible to oxidative stress due to their high activity levels and consumption of oxygen (d'Apolito et al., 2018; Lu et al., 2014). Regarding inflammation, generalized dysfunction of the NVU reduces function of both astrocytes and neurons, resulting in a pro-neuroinflammatory state (Jadavji et al., 2015).

2.3.1 Neurovascular Unit and Alzheimer's Disease

Recent studies suggest impairment of the NVU may be a significant contributor to the development of AD. As mentioned previously, the NVU plays an important role in maintaining integrity of the BBB and regulating CBF (Sweeney, Kisler, et al., 2018). Research suggests increased permeability of the BBB and reduced CBF (Yu et al., 2020), both of which are consequences of a disrupted NVU, contribute to amyloid-beta accumulation in the brain (Sweeney, Kisler, et al., 2018).

BBB disruption is an emerging theory as a pathway to AD onset (Arvanitakis et al., 2016; Sweeney, Sagare, et al., 2018), as BBB integrity appears to be impaired in those with AD (Yamazaki & Kanekiyo, 2017). Evidence from neuroimaging studies suggests the BBB can become comprised in the hippocampus, relatively early in the aging process, which in turn contributes to cognitive changes (Barry Erhardt et al., 2019; Montagne et al., 2015; Nation et al., 2019). Furthermore, results from postmortem studies indicate greater amounts of plasma proteins in the cortex of AD brains and greater BBB permeability in patients with mild cognitive dysfunction (Montagne et al., 2015).

In AD, there appears to be an overall reduction in the ability for crucial proteins, such as, but not limited to, low-density lipoprotein receptor 1 (LRP1) and p-glycoprotein (P-gp) (Yamazaki & Kanekiyo, 2017; Zenaro et al., 2017), to transport amyloid-beta across the BBB (Yu et al., 2020). As a result, there is diminished amyloid-beta clearance (Govindpani et al., 2019). A β_{42} has been associated with disruption in TJ organization and junction with endothelial cells (Carrano et al., 2011; Carrano et al., 2012; Zlokovic, 2011); in other words, disruption of the NVU. The NVU can be affected in other ways. For example, astrocyte end-feet retract and swell in response to amyloid-beta burden, which results in impairment in brain function and

metabolism (Merlini et al., 2011). Reductions in pericyte coverage have also been noted in response to amyloid-beta burden, exacerbating cerebral hypoperfusion and aiding in diminished amyloid-beta protein clearance (Dalkara et al., 2011).

In addition to BBB disruption, patients with AD display changes in CBF decades before clinical symptoms are observable (Binnewijzend et al., 2016; Dong et al., 2018; Hays et al., 2016). The cholinergic-vascular hypothesis is widely accepted to explain CBF reductions in AD (Govindpani et al., 2019; Yu et al., 2020). At autopsy, AD brains exhibit evidence for severely reduced cholinergic innervation in numerous brain regions, including the hippocampus and temporal cortex (Francis et al., 1999). According to this hypothesis, the reduction in cholinergic innervation is partially due to the significant loss of many cholinergic neurons, commonly observed in AD (Govindpani et al., 2019), which may explain CBF reductions. In concordance with reduced cholinergic innervation, neurovascular uncoupling contributes to reduced CBF (Yu et al., 2020). This will be discussed in greater detail in the subsequent section (*Two-hit Vascular Hypothesis*). Other vascular abnormalities contributing to reduced CBF include morphological changes in arterioles, reduced string vessel function, increased amyloid-beta production, and insufficient amyloid-beta clearance, as summarized by Yu et al. (2020).

Among the neuropathologic features of AD (i.e., amyloid-beta plaques and tau tangles), include other risk factors, one of which is vascular health. Vascular risk factors that increase risk for AD include cardiovascular disease (e.g., stroke, atrial fibrillation, coronary heart disease, and heart failure), large and small vessel disease, hypertension, arterial stiffness, diabetes, hypercholesterolemia, high homocysteine levels, and obesity (de Bruijn & Ikram, 2014). At autopsy, there is observable vascular damage commonly found in addition to the hallmark amyloid-beta plaques and tau-tangles (Blennow et al., 2006; Cui et al., 2014; Cukierman et al.,

2005; Haan & Wallace, 2004). In fact, a large autopsy-based neuropathological study estimated approximately 80% of patients diagnosed with AD, with no evidence of mixed/vascular dementia while living, had vascular pathology (Toledo et al., 2013). Specifically, there was evidence for cortical infarcts (stroke), lacunes (multiple small infarcts), cerebral microbleeds (small cerebral hemorrhages), and multiple microinfarcts, like small vessel disease, arteriolosclerosis, perivascular spacing, intracranial atherosclerosis, and cerebral amyloid angiopathy (Toledo et al., 2013).

In summary, research findings characterize vascular and neurovascular damage as risk factors for AD and dementia pathophysiology (van de Haar et al., 2016). Observable vascular pathology further supports the theory that cerebrovascular dysfunction is commonly present in AD (Sweeney et al., 2019) and the NVU is disrupted. NVU dysfunction creates a chain of negative consequences including neuroinflammation, oxidative stress, NO deficits, reduced CBF, and increased BBB permeability (Iadecola, 2013; Lyros et al., 2014; Montagne et al., 2015). Therefore, understanding the role of vascular health may be important for addressing neurodegeneration and associated decline characterized by AD.

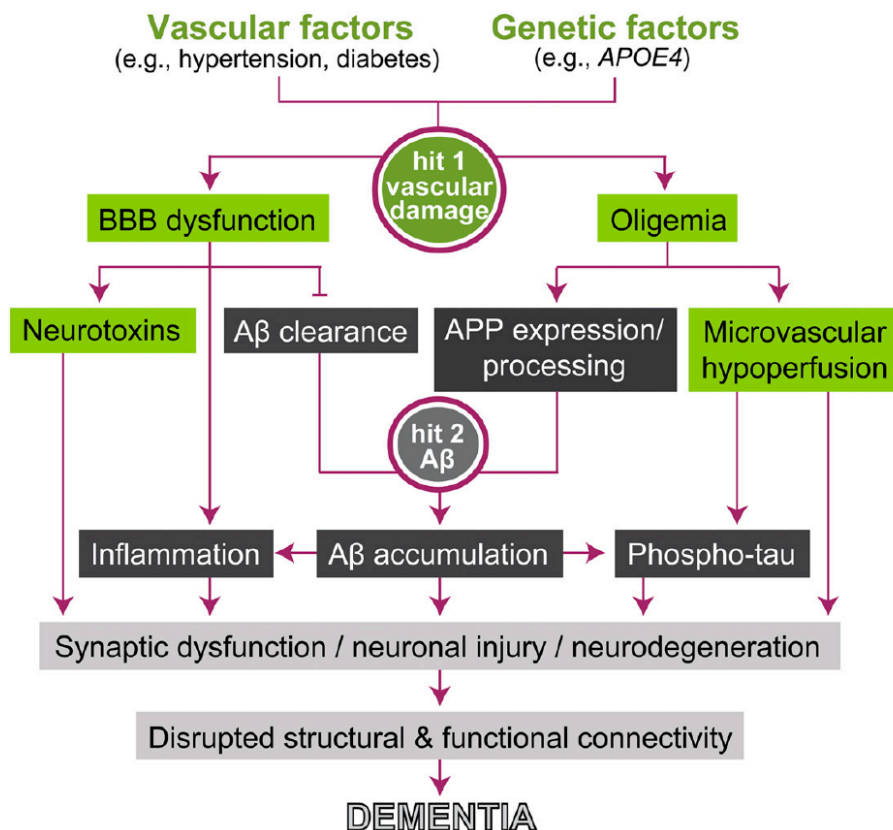
2.3.2 Two-hit Vascular Hypothesis

To account for the vascular risk factors in the development of AD and inconsistencies associated with the Amyloid Cascade Hypothesis, an alternative hypothesis for AD pathology was proposed. The Two-hit Hypothesis (Zhu et al., 2004) suggests there are two factors contributing to the development of AD: (1) the presence of a steady state: after the pathogenic process has been initiated by hit 1 and hit 2, neurons recruit permanent changes to adapt, which results in a new oxidative steady state; and (2) neuronal compensatory potential is depleted: the new oxidative steady state requires recruitment of compensatory mechanisms, which depletes the

overall compensatory potential to fight additional insults, and this makes neurons more vulnerable to secondary insults (Zhu et al., 2007; Zhu et al., 2004). For a visual representation of the Two-hit Vascular Hypothesis, see Figure 2.

Figure 2

Two-hit Vascular Hypothesis



Note. Figure from Nelson et al. (2016). BBB = blood brain barrier; A β = amyloid-beta; APP = amyloid precursor protein.

As summarized by Nelson et al. (2016), initial insults (Hit 1) caused by cerebrovascular damage triggers neurodegeneration and neuronal injury. Resulting consequences include reduced CBF and BBB disruption, which leads to secondary accumulation of neurotoxins and brain hypoperfusion (Sagare et al., 2013; Zlokovic, 2011). CBF is important for delivering nutrients

and oxygen to the brain. Therefore, reduced CBF results in reduced energy metabolism (Iadecola, 2013). Cerebral hypoperfusion, or reduced blood flow to the brain, can impair protein synthesis, in turn affecting synaptic plasticity (Iadecola, 2004). Additionally, hypoperfusion can lead to neurochemistry imbalances, resulting in edema, white matter lesions, and neuronal death (Zlokovic, 2011).

Initial vascular insults have many consequences. Among the consequences includes neurovascular uncoupling (Nelson et al., 2016), which is defined as alterations in blood perfusion in response to neuronal activity (Iadecola, 2013; Lecrux & Hamel, 2011). As mentioned previously, neurovascular uncoupling contributes to reduced CBF (Yu et al., 2020). As such, there is a close, dependent relationship between CBF and neuronal activity (Lecrux & Hamel, 2011). When the arteries supplying the blood flow to the brain are diseased or impaired, their response to neuronal activity can be negatively impacted. In other words, the typical neurovascular relationships are dismantled (Mikulis, 2013). As a result, CBF is consequently reduced in response to neuronal activation (Mikulis, 2013). Neurovascular coupling is a beneficial mechanism for the brain, as it ensures the brain is receiving an adequate supply of oxygen and glucose, as summarized by Lecrux and Hamel (2011). Therefore, inadequate CBF volume and velocity (due to neurovascular uncoupling) reduces the amount of oxygen and glucose supplied to neurons (Lecrux & Hamel, 2011), depriving the brain of necessary energy.

Initial vascular insults (Hit 1) and associated consequences lead to the brain experiencing oxidative stress, which is a pervasive feature of AD in all stages. Oxidative stress, however, is not necessarily unique to AD, and in tolerable amounts, oxidative stress is acute (LeBel & Bondy, 1992; Zhu et al., 2004). The brain implements compensatory strategies to elicit changes that maintain neuronal homeostasis (LeBel & Bondy, 1992; Zhu et al., 2004). It is when

oxidative stress becomes pervasive, persisting over time, that forces neurons to make adaptive changes. When oxidative stress is pervasive, the brain is in an “oxidative steady state” (LeBel & Bondy, 1992; Zhu et al., 2004). Because neurons are dedicating extensive resources to prevent additional oxidative stress in the “oxidative steady state,” the brain is more susceptible to secondary insults that require additional implementation of compensatory strategies (Zhu et al., 2004).

Secondary insults lead to increased sensitivity triggering a new oxidative steady state, which may serve as the second hit. As summarized by Zhu et al. (2004), the result is a cascade effect of AD-related changes (Allen et al., 1991; Connor et al., 1996; Crutcher et al., 1993). AD-related secondary insults include impaired amyloid-beta clearance (Nelson et al., 2016) and increased production of amyloid-beta protein (Ramanathan et al., 2015; Zlokovic, 2011). Overall, the literature indicates vascular health is important for brain health and can result in several consequences including BBB dysfunction, permeated neurotoxins, neuroinflammation, impaired amyloid-beta clearance and increased production, and reduced CBF. Furthermore, these vascular consequences likely contribute to neuropathological changes associated with AD and are important to consider when establishing interventional methods.

2.3.3 Alzheimer’s Disease and Vascular Dementia

Vascular pathology complicates the characterization of clinical and neuropathic changes that occur in AD. There is extensive literature examining AD and VaD as two distinct forms of dementia; however, distinguishing between them can be challenging, due to shared clinical presentations and pathology. VaD is the second leading type of dementia after AD, accounting for 17-20% of all dementia patients (Plassman et al., 2007). Generally, VaD is caused by reduced CBF to brain areas resulting in inadequate blood supply, or ischemia (Uwagbai & Kalish, 2021).

There is a wide range of etiologies including multi-infarct dementia characterized by multiple small strokes, single infarct dementia caused by a single major stroke, and small vessel disease (Venkat et al., 2015). Regardless of the specific cerebrovascular accident, the disruption in brain circuits or damage to associated brain areas (Zhao et al., 2014) can result in a VaD process. Not surprisingly, associated risk factors for VaD include, but are not limited to, hypertension, diabetes, cardiac disorders, atherosclerosis, stroke, and metabolic syndrome, as summarized by Venkat et al. (2015).

The symptom presentation (Venkat et al., 2015) and neuropathological changes may be quite heterogeneous (Tariq & Barber, 2018) depending on the underlying cause of VaD. The brain has vasoregulatory mechanisms to ensure the brain receives adequate blood flow to support energy production among cells (Venkat et al., 2015). Consequences of cerebrovascular events include decreased CBF, hypoxia, oxidative stress, and inflammatory response. In turn, these events can cause mitochondrial dysfunction, neuronal damage, endothelial dysfunction, BBB leakage, demyelination, and neurovascular uncoupling (Venkat et al., 2015).

Vascular contributions to cognitive impairment and dementia (VCID) is a term used to characterize the role of vascular risk and lesions on cognition. It is clearly established that AD and VaD share vascular risk factors contribute to the development of cognitive impairment and neurodegenerative process. In fact, most clinical AD cases, especially in patients over 80 years, have both classic AD pathology (amyloid-beta plaques and hyperphosphorylated tau tangles), along with vascular pathology (Dodge et al., 2017). Some studies suggest that the dichotomous criteria (AD vs. VaD) do not reflect true clinical patient presentations (Kalaria, 2002; Neuropathology Group. Medical Research Council Cognitive & Aging, 2001; Nolan et al., 1998; Snowden et al., 1997). For example, a prospective autopsy study examining 87 patients revealed

that out of the 13 patients clinically diagnosed with VaD, 6 out of 13 patients had AD alone, and 6 had both AD and cerebrovascular disease pathology (Nolan et al., 1998). Other studies have found more than 40% of patients who met clinical criteria for VaD had AD pathology at autopsy (Kalaria, 2002) and 38% had AD pathology, as well as evidence for cerebral infarcts (Schneider et al., 2007). These findings provide support for the hypothesis that the dichotomous clinical criteria likely do not reflect true dementia pathology. As such, the overlapping clinical and pathological features should be considered.

When the NVU fails to cope with vascular insults, cognitive decline can result (Snyder et al., 2015) and could be considered VCID. Research suggests when vascular pathology is present in AD, there appears to be less AD-specific pathology, but the same level of cognitive impairment overall (Dodge et al., 2017). These findings suggest vascular pathology significantly contributes to cognitive difficulties in AD (Dodge et al., 2017). Therefore, focusing exclusively on VaD when vascular risk factors are identified can distract from the importance of vascular pathology in other forms of dementia, such as AD (Cavalieri & Schmidt, 2010). VCID mechanisms are not well understood, but hypothesized mechanisms underlying VCID include hypoperfusion and hypoxia, increased BBB permeability, endothelial dysfunction, systemic inflammation, oxidative stress, and trophic uncoupling (Hachinski et al., 2019; Iadecola, 2013). Consequently, it is important to consider vascular factors in understanding pathophysiological changes associated with the various dementia (Cavalieri & Schmidt, 2010).

CHAPTER 3

RISK FACTORS FOR ALZHEIMER'S DISEASE

3.1 Age

Age is arguably, the number one risk factor for AD (Nelson et al., 2016). Most people diagnosed with AD are 65 years and older ("2023 Alzheimer's disease facts and figures," 2023) and the incidence of AD increases with age. Aging is marked by the accumulation of degenerative processes that occur throughout the body (Wagner et al., 2016). The degenerative process is characterized by changes in molecular pathways leading to compromises in cell tissue and function (Bratic & Larsson, 2013; Kirkwood, 2005). Overall, the process of aging and changes associated with aging are still not completely understood; however, scientists agree the causes of many non-communicable diseases (NCDs) that occur later in life are likely caused by the following: DNA damage, alterations in gene and non-coding RNA expression, genotoxicology, oxidative stress, and/or shorter telomeres (Franzke et al., 2015; Lovell & Markesbery, 2007; Martin-Ruiz et al., 2006). Importantly, it appears the aging process is multifactorial and therefore, not one single factor can provide a valid measurement for aging (Wagner et al., 2016).

The physical manifestations of aging are widespread, and the brain is no exception to the aging process. At the most basic level, neurodegeneration is defined as the loss of structure and function in neurons (Przedborski et al., 2003). Structurally, the aging brain is classically characterized by gray and white-matter atrophy, with most gray matter reductions in the frontal and temporal lobes (Jack et al., 1997), along ventricular enlargement due to neuronal loss (Apostolova et al., 2012) and global cerebral atrophy (Schoenberg & Duff, 2011). At the cellular

level, aging characteristics include reduced DNA repair, abnormal molecular waste disposal, mitochondrial dysfunction, oxidative damage, neuronal calcium dysregulation, impaired adaptive stress response, inflammation, stem cell exhaustion, and abnormal neuronal network activity (Mattson & Arumugam, 2018).

Functional brain changes, resulting from structural changes, often manifest in cognition. Healthy aging is associated with progressive reductions in learning and memory, attention, processing speed, sensory perception, motor coordination (Alexander et al., 2012; Dykiert et al., 2012; Levin et al., 2014), executive functioning, task switching, and episodic memory (Alexander et al., 2012). If the rate and extent of neurodegeneration extends beyond what is expected of normal aging (impairments in cognition and daily functioning), it may be indicative of a degenerative process, such as dementia (Jack et al., 2005).

There continues to be many unanswered questions about the aging brain including the rate of change, associated pathological and functional changes, and existing protective and risk factors for aging and cognitive impairment. As a result, scientists have proposed numerous theories of cognitive aging including Inhibition Theory, Processing Speed Theory of Aging, Dedifferentiation Theory, Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH), Posterior-Anterior Shift in Aging (PASA), Scaffolding Theory of Cognitive Aging (STAC), and Scaffolding Theory of Cognitive Aging Revised (STAC-r) to characterize age-related changes. These models will be discussed briefly in subsequent sections. For full review, please see existing literature (Hasher & Zacks, 1988; Salthouse, 1996; Li & Lindenberger, 1999; Cabeza et al., 1997; Berlingeri et al., 2013; Grady et al., 1994; Park & Reuter-Lorenz, 2009).

3.1.1 Inhibition Theory

Older adults are more likely to have attentional difficulties compared to young adults and in general, with attentional declines beginning at age 60 (Treitz et al., 2007). To better understand this relationship, Hasher & Zacks (1988) proposed the inhibition theory, as summarized by Hasher and colleagues (1991). This model proposes inhibition is a central mechanism for determining the contents of working memory, which can in turn impact various domains of cognitive function (Hasher et al., 1991; Hasher & Zacks, 1988). In other words, inhibition is one of the primary mechanisms interconnecting attention, memory, and language among other neurocognitive processes. According to this model, there is active selection of or an excitation process that encourages stimulus processing. Simultaneously, inhibition, or active suppression of certain stimuli, influences the content of working memory or other memory processes (Hasher et al., 1991). A diminished inhibitory system will expand the number of activated contents at encoding, and in turn, less stimuli will be excluded or suppressed. Irrelevant stimuli, previously suppressed, that are now activated will receive richer processing. Likewise, ineffective inhibition will also prevent suppression of irrelevant information retrieval pathways (Hasher et al., 1991). For example, when reading, older adults may be more likely to interpret material that is not necessarily crucial to the meaning of the provided passage (Hamm & Hasher, 1990). Therefore, older adults may encode irrelevant information, rather than relevant stimuli.

3.1.2 Processing Speed Theory of Aging

In contrast to the inhibition theory, the processing speed theory of aging accounts for age-related changes in cognitive functioning to diminished processing speed (Salthouse, 1985). As summarized by Salthouse (1996), this theory suggests performance on some cognitive tasks may

be dependent upon the efficiency or effectiveness of processing. Therefore, limiting processing abilities could negatively impact functioning of other cognitive domains (Salthouse, 1996).

Increased age is one potential constraint on the speed of cognitive processing (Salthouse, 1996). Reduced cognitive processing speed could be due to two factors: (1) diminished function and activity; or (2) diminished ability to carry out functions rapidly and efficiently (Salthouse, 1996). Although it is not the only contributor to age-related changes in cognition, it is likely reduced processing speed has a major impact on numerous domains of cognitive function (Salthouse, 1980, 1985; Salthouse, 1992, 1994), such as working memory (Salthouse, 1991).

3.1.3 Dedifferentiation

The dedifferentiation theory was proposed to better understand the mechanisms behind age-related brain and cognitive changes (Li & Lindenberger, 1999), although it remains a controversial theory (Koen & Rugg, 2019). Dedifferentiation occurs when cognitive abilities cluster to create a more general ability structure, and they do not have distinguished or differential patterns. In contrast, differentiation suggests cognitive abilities are broken down into groups or clusters of similar abilities (e.g., processing speed). These clusters or domains are associated with distinguished patterns of brain activity (Li & Lindenberger, 1999).

Importantly, the organization of cognitive abilities and behavior changes across the lifespan is associated with different developmental stages, yielding potential evidence for various degrees of differentiation, or lack of differentiation, among various cognitive abilities (Burt, 1954; Garrett, 1946; Reinert, 1970; Spearman, 1927). Generally, there appears to be an overall lack of differentiation early in life (e.g., early childhood) resulting in cognitive abilities existing as a large general structure. As people get older, cognitive abilities become more differentiated (clustering into distinct domains with unique patterns of activation). Ultimately, however,

cognitive abilities become dedifferentiated (existing as a large general structure with no distinct patterns of activation) with old age (Li & Lindenberger, 1999). The factor analytic structure of cognitive function also indicates an age-related increase in the amount of variance that is shared amongst factors (Cunningham, 1980) and the strength of correlations among cognitive abilities in older individuals tend to be stronger, compared to younger individuals (Baltes & Lindenberger, 1997). This finding further suggests dedifferentiation in older age. Functional neuroimaging studies also suggest age-related changes in brain activation coinciding with the (de)differentiation of cognitive abilities. Specifically, the older brain may rely on support from other networks, that were previously independent at younger ages. In other words, there is stronger dependence amongst brain networks with age (Grady et al., 1994; Li & Lindenberger, 1999) and patterns of activation become less distinguished.

3.1.4 Hemispheric Asymmetry Reduction in Older Adults Model

The hemispheric asymmetry reduction in older adults (HAROLD) model, proposed by Cabeza and colleagues (1997) posits there is greater bilateral activity in the prefrontal cortex (PFC) in older adults, compared to young adults (Cabeza et al., 1997) performing the same task. Originally, the authors attributed this finding to functional compensation. According to this view, bilateral activity in the PFC increases with age in order to compensate for age-related neurocognitive deficits (Cabeza et al., 1997). With more evidence, researchers argue the age-related changes may be more likely to reflect hemispheric asymmetry due to general aging, rather than task-specific changes (Cabeza, 2002). As such, these findings support that under similar circumstances, PFC activity during a cognitive task is less lateralized in older adults, relative to young adults. In support of this model, additional research has found evidence for age-related asymmetry across episodic and semantic memory (Backman et al., 1997; Berlingeri et al.,

2013; Cabeza, 2002; Cabeza et al., 1997; Cabeza & Nyberg, 2000; Nyberg et al., 1996; Tulving et al., 1994) and working memory (Cabeza, 2002; Reuter-Lorenz et al., 2000), further suggesting greater bilateral activity in older adults.

3.1.5 Compensation-Related Utilization of Neural Circuit Hypothesis

With the greater emergence of functional neuroimaging evidence, the HAROLD model has been reassessed, as inconsistencies emerged with the HAROLD effect/pattern of activation. For example Manenti et al. (2011) observed the HAROLD effect only in the encoding phase of a paired associated memory task and argued it was a characteristic of cognitively high performing older adults. Additionally, a study conducted by Duverne et al. (2009) observed the HAROLD pattern during encoding of a memory task. Overall, the predictability of PFC activation and associated age-related changes proves to be more difficult than previously hypothesized, as evidenced by findings that suggest the HAROLD model captures only some age-related activity patterns associated with the aging process (Berlingeri et al., 2013). Some researchers argue age-related changes in brain activation are more consistent with the compensation-related utilization of neural circuits hypothesis (CRUNCH) (Berlingeri et al., 2013).

The CRUNCH model proposes increased activation in older adult brain regions, regardless of hemisphere, is observed on easier versions of the same task (Reuter-Lorenz & Cappell, 2008). As task demands increase, older adults eventually reach a plateau at their highest level of activation. Once people meet their peak activation but task demands continue to increase, performance declines because task demands cannot be met (Reuter-Lorenz & Cappell, 2008). Overactivation in older adult brains may be indicative of a compensation process, that the involved brain regions are “working harder” compared to young adults (Reuter-Lorenz & Cappell, 2008). In other words, overactivation can compensate for when information input is

compromised, and for reduced cognitive efficiency or processing deficits by recruiting other brain networks (Persson et al., 2007; Reuter-Lorenz & Cappell, 2008). Network recruitment is the brain's attempt to employ more neural resources to improve output (Reuter-Lorenz & Cappell, 2008). Overactivation is not always beneficial, however, as it is also associated with poorer cognitive performance (Reuter-Lorenz & Cappell, 2008) and the underlying mechanisms for the relationship between overactivation and poor performance are somewhat unclear. There have been hypothesized mechanisms which include using multiple cognitive strategies, implementing inefficient coping strategies, or the presence of disinhibition and dedifferentiation (Reuter-Lorenz & Cappell, 2008). Regardless of underlying mechanisms, overactivation in older adults is the result of the brain "working harder" and needing to recruit additional neural networks in attempt to improve output, even if better performance is not always the outcome.

3.1.6 Posterior-Anterior Shift in Aging

Originally proposed by Grady et al. (1994), the posterior-anterior shift in aging (PASA) model proposed younger adults display weaker activity in occipitotemporal regions, but greater activation in anterior regions including the PFC. Grady and colleagues (1994) first saw this pattern in tasks examining face and location perception. Since that time, researchers have examined the PASA pattern of activation in several domains including attention, visual perception, visuospatial processing, working memory, along with episodic memory encoding and retrieval (for review see Davis et al., 2008). Additional evidence has confirmed the validity, function, and generalizability of PASA. Specifically, research indicates age-related reduction in occipital activity is coupled by age-related increase in PFC activity, regardless of task difficulty (Davis et al., 2008). Furthermore, occipital activity reduction is negatively correlated to increased PFC activity and the same neuroimaging study, in fact, revealed a positive correlation

between increased PFC activity and cognitive performance (Davis et al., 2008). These findings suggest PASA patterns serve as a compensatory function. Therefore, to understand age-related activation changes, the PASA model and hypothesized activation patterns are worth considering.

3.1.7 Scaffolding Theory of Cognitive Aging

The brain can be characterized as a dynamic part of the human body and like other organs, it has a desire to establish and maintain homeostasis (Park & Reuter-Lorenz, 2009). As humans age, this drive to maintain homeostasis continues, despite structural and functional changes. As summarized by Park and Reuter-Lorenz (2009), age-related cognitive changes include reduction in processing speed, working memory, inhibition, attentional abilities, and effortful control. Structurally, neuroimaging studies reveal volumetric shrinkage across the lifespan occurring in a variety of brain regions, such as the caudate, cerebellum, hippocampus, and prefrontal areas. Other areas of the brain, however, experience minimal volumetric loss (e.g., the entorhinal and the visual cortex) with age. Also, important to note is cortical thinning that occurs across the lifespan, with global cortical thinning beginning as early as middle age. Other age-related structural changes include the presence of white matter hyperintensities (WMH) and reduced numbers of dopaminergic receptors (Park & Reuter-Lorenz, 2009).

To understand age-related cognitive, structural, and functional changes, the scaffolding theory of cognitive aging (STAC) model has been proposed (Park & Reuter-Lorenz, 2009). The overarching goal of STAC was to understand age differences in cognitive functioning, while considering biological and neuropsychological factors (Reuter-Lorenz & Park, 2014). Scaffolding captures the flexibility and dynamic nature of the brain's response to normal aging and associated challenges throughout the lifespan (Park & Reuter-Lorenz, 2009). For example, when learning a new skill, the brain recruits multiple networks and circuits required for skill

acquisition and task performance (Petersen et al., 1998). As the skill is acquired, performance becomes less effortful. Once a skill is overlearned, the broad neural circuits originally recruited transition to becoming more specific. To maintain level of output in the context of structural and function deterioration that occurs with age, the brain must recruit additional circuits to assist impaired structures (Park & Reuter-Lorenz, 2009). As summarized by Park and Reuter-Lorenz (2009) there is greater bilateral activation and overactivation in frontal networks in older adults; therefore, the recruitment of other networks to meet task demands reflects compensatory scaffolding (Park & Reuter-Lorenz, 2009). In other words, scaffolding can provide supplementary, complementary, and alternative ways to achieve an output goal (Park & Reuter-Lorenz, 2009).

Like other models, STAC was reexamined, as more research has been conducted and neuroimaging techniques improved over time. The original STAC model predicted cognitive function at a single point in time during the lifespan but failed to account for the life-course and its associated influences on cognitive aging (Reuter-Lorenz & Park, 2014). As a result, STAC was revised (STAC-r) to incorporate variables that occur throughout the lifespan which have impacts on both brain structure and function (Reuter-Lorenz & Park, 2014). STAC-r considers positive influences on brain structure and function, also known as neural resource enrichment (Reuter-Lorenz & Park, 2014). Factors in this category may include participation in cognitive, leisure, and social activities, along with higher levels of education, and cardiovascular fitness (Reuter-Lorenz & Park, 2014). STAC-r also incorporates variables that have negative influences on brain structure and function, such as neural resource depletion (Reuter-Lorenz & Park, 2014). Factors having a negative influence on the brain, according to this model, include the presence of APOE-e4, presence of vascular risk factors, and stress (Reuter-Lorenz & Park, 2014).

Overall, there are structural and functional brain changes, as well as cognitive changes associated with age. To understand and explain these changes, the theories of cognitive aging have been proposed (Inhibition Theory, Processing Speed Theory of Aging, Dedifferentiation Theory, HAROLD model, CRUNCH, PASA, STAC, and STAC-r). Arguably, if researchers can better understand the typical changes associated with age, predicting changes that extend beyond what is typical for “normal” aging may become easier.

3.2 Race and Ethnicity

Cross cultural neuropsychology aims at characterizing culture related variables, such as race and ethnicity, and their influence on brain-behavior relationships among neurological and neuropsychiatric populations. Like many areas of research, marginalized groups are considerably underrepresented in the field of AD and related dementia research. Unfortunately, underrepresentation of minority groups in research has several consequences including, but not limited to, inaccurate diagnoses and inconsistent classification ultimately leading to incorrect conclusions (Rosselli et al., 2022). These consequences remain especially true for the field of AD and related dementia research, as black/African American and Hispanic older adults are disproportionately more likely to have AD or other dementias compared to non-Hispanic white older adults in the United States (Demirovic et al., 2003; Dilworth-Anderson et al., 2008; Harwood & Ownby, 2000; Manly & Mayeux, 2004; Perkins et al., 1997; Power et al., 2021; Steenland et al., 2016). Research has attempted to characterize the prevalence of AD of different ethnoracial subgroups. However, these estimates are variable depending on sample characteristics. Matthew and colleagues (2019) examined prevalence rates among different racial and ethnic groups among beneficiary (Medicare Fee-for-Service) and US Census Bureau older adult populations. Results revealed that among Medicare beneficiaries, prevalence rates were

14.7% for black/African Americans, 12.9% for Hispanics, 11.3% for non-Hispanic whites, 10.5% for American Indian or Native Alaskan, and 10.1% for Asian or Pacific Islanders. Among US Census groups, results revealed prevalence rates of 13.8% for black/African Americans, 12.2% for Hispanics, 11.5% for individuals belonging to two or more ethnorracial groups, 10.3% for non-Hispanic whites, 9.1% for American Indian or Native Alaskan, and 8.4% for Asian or Pacific Islanders (Matthews et al., 2019). In a more recent study examining data from the Chicago Health and Aging Project (CHAP), results indicated prevalence rates of AD in adults age 65 and older to be 19% for black/African Americans and 14% for Hispanic individuals, and 10% for white older adults (Rajan et al., 2021).

To understand why there are differences in prevalence rates among different ethnorracial groups, researchers have examined whether differences are attributable to fixed biological/genetic factors or fluid cultural differences. Race and ethnicity are commonly associated with unique biological and genetic differences. Large epidemiology studies have attempted to capture genetic factors among different racial groups that may differentially impact health risk and outcomes, which raises the question of genome-wide risk for AD. As summarized by Kunkle and colleagues (2021), in a large genome-wide association study including over 5,000 black/African American individuals from the Alzheimer Disease Genetics Consortium, the presence of various genetic factors, such as ABCA7 and APOE, have been confirmed. Research also suggests differences in odds ratios, or the likelihood of gene expression, between black/African American and non-Hispanic White individuals, as well as differing intergenic (stretch of DNA sequence between genes) regions at certain genes (Kunkle et al., 2021; Reitz et al., 2013). A recent meta-analysis suggests molecular pathways implicated in AD overlap significantly between black/African American and non-Hispanic white individuals; however, the

exact locations of the brain within these pathways important for disease onset may differ (Kunkle et al., 2021). In addition, research suggests more novel pathways for AD disease onset in black/African Americans. More specifically, Kunkle and colleagues (2021) identified that while amyloid and tau pathology may be important for non-Hispanic white individuals, it did not emerge as a top pathway to disease onset for black/African Americans, rather, the kidney system may be a more important mechanism. This is a novel finding and reasons why this pathway became significant is not completely understood. However, some research indicates black/African Americans are three times more likely to experience kidney failure (Laster et al., 2018) and furthermore, impairments in the kidneys ability to clear amyloid-beta circulating hormones is associated with an elevated risk of cerebral amyloid-beta retention (Pirici et al., 2017). Furthermore, additional research has suggested that AD may not progress at the same pace in black/African Americans as connectivity between medial temporal lobes and dorsomedial subsystems appears to be modified by race (Kenny et al., 2012; Misiura et al., 2020; Wang et al., 2006). In other words, greater cognitive impairment is associated with increased connectivity (rather than decreased connectivity) in non-Hispanic white subjects (Misiura et al., 2020).

Some research suggests race should not be viewed as a fixed genetic characteristic and although there are genetic differences, such as those seen related to APOE e4 risk (see *Genetic Factors* section for more detailed literature review), the genetic factors do not account for large difference across groups (Alzheimer's Association [AA}, 2023). In contrast, health disparities among ethnoracial groups have been emphasized while also recognizing disparities have not been fully incorporated in research (Rosselli et al., 2022). Performance on cognitive testing has been strongly linked to cultural factors, partially due to the reliance of learned academic material

(e.g., vocabulary knowledge), literacy (e.g., reading), and cultural factors (e.g., culturally salient pictures). For example, research suggests that high levels of US acculturation are associated with better cognitive performance among older, low-socioeconomic status Latinos (Martinez-Miller et al., 2020). Furthermore, in a sample where participants did not differ in vascular or brain biomarkers, black/African Americans scored lower at baseline on cognitive testing and declined faster upon examination of longitudinal analysis than non-Hispanic whites, even after low educational attainment and premorbid reading ability were adjusted for statistically (Amariglio et al., 2020).

The research finding suggesting that ethnoracial factors, such as language, education, and culture, modulates performance on neuropsychological testing likely contributes to the lack of normative data across the various racial and ethnic groups (Babulal et al., 2019; Rosselli et al., 2022). Health disparities, such as reduced access to health care and early screening assessments, and reduced educational attainment, are lower in ethnoracial groups (Vega et al., 2017).

Disparities have been proposed to predominantly account for the various prevalence rates in AD. Cultural factors among ethnoracial groups become especially important considering these factors have been reported to influence cognitive reserve, biological markers (neuroimaging and biofluid), immunity, and neurodegeneration in addition to neuropsychological test performance (Babulal et al., 2019).

Whether the genetic/biological factors or health disparities are primarily responsible for AD risk, onset, and progression across ethnoracial groups, understanding the influence of these factors is likely multifactorial. Regardless, the underrepresentation of ethnoracial groups in AD research remains a critical limitation as researchers attempt to understand the unique risk among

cultural groups within and outside the United States. As such, sample demographics should be examined carefully, and researchers should refrain from overgeneralizing research findings.

3.3 Genetic Factors

3.3.1 Genetic Mutations

As mentioned previously, EO-FAD is an autosomal-dominant disorder, accounting for less than .5% of AD cases (James & Bennett, 2019), and marked by one of the following genetic mutations APP, PS-1, PS-2 (Tanzi, 2012). LO-SAD represents most cases of AD and is influenced by both genetic susceptibility and environmental risk (Lambert & Amouyel, 2011). There are no established genetic mutations in LO-SAD, but there are several major genetic risk factors, including the presence of APOE-e4 alleles (Corder et al., 1993; Strittmatter, Saunders, et al., 1993). Suspected mechanism for which APOE-e4 status increases risk for AD is discussed in the subsequent section.

3.2.2 Apolipoprotein Genotype

One of the most well-established genetic risk factors for LO-SAD is apolipoprotein (APOE) (James & Bennett, 2019). Although APOE genotype has no significant effect on disease duration, up to 60% of individuals diagnosed with AD have at least one e4 allele (Farrer et al., 1997). APOE is a protein that facilitates lipid transport throughout the body (Cole et al., 2010). It plays a key role in mobilizing cholesterol between cells and redistributing cholesterol within cells (Riedel et al., 2016). Cholesterol transport promotes maintenance of myelin and neuronal membranes in the CNS and PNS (Leduc et al., 2010). Important for AD pathology, amyloid-beta is carried by lipids, similar to APOE (Cole et al., 2010). Every individual inherits one of three alleles from each parent: e2, e3, and e4. As a result, there are six possible pairs that can be

inherited. Possessing the e4 allele increases risk for developing AD. In fact, inheriting just a single copy of the e4 allele increases the risk for developing AD by three-fold, while inheriting two copies of the e4 allele increases risk by eight- to 12-fold (Holtzman et al., 2012; Loy et al., 2014; Michaelson, 2014). Not only does the overall risk for developing AD increase, but those with two copies of the e4 allele are more likely to develop AD at a younger age compared to those with e2 or e3 alleles (Spinney, 2014). A meta-analysis including a United States sample, found that 56% who had been diagnosed with AD also had at least two copies of the APOE-e4 gene, whereas 11% diagnosed with AD only had one copy (Ward et al., 2012). Important to note, however, is that although the presence of the APOE-e4 gene increases risk, it does not guarantee the development of AD.

There have been several suspected mechanisms proposed to understand how the e4 allele contributes to increased risk of AD. First, the structure of the e4 allele is different compared to other alleles. The C-terminal domain of APOE is predicted to form helices, which encourage lipid binding (Mahley & Rall, 2000; Weisgraber, 1994). More specifically, APOE-e4 alleles are more compact (Dong & Weisgraber, 1996; Dong et al., 1994) and facilitate domain interactions, which may be responsible for resulting pathological effects (Mahley et al., 2009). The e4 structure results in elevated risk for plasma cholesterol, low density lipoprotein (LDL) levels (Mahley et al., 2009), and presence of cardiovascular disease (Mahley & Rall, 2000). Additionally, the three alleles vary in their binding affinities to amyloid-beta (Riedel et al., 2016). APOE-e4 increases amyloid-beta deposition and formation of amyloid-beta oligomers, while also negatively impacting glucose metabolism (Riedel et al., 2016). Mice models suggest the e4 allele is associated with breakdown of the BBB (Montagne et al., 2020) and tau accumulation (Bennett et al., 2013). Furthermore, APOE-e4 increases production of reactive

oxygen species (ROS), which in turn leads to increased oxidative stress resulting in a neurotoxic environment (Riedel et al., 2016).

Regarding APOE-e4 risk, certain populations have greater risk. Some studies suggest black/African American populations may be more likely to inherit an e4 allele compared to European Americans (Evans et al., 2003; Rajan et al., 2017). Although the presence of the e4 allele may be more likely in black/African American populations, the associated risk status is inconsistent in the literature. For example, some research suggests the possession of an e4 allele did not increase risk of developing AD in black/African Americans (Evans et al., 2003; Tang et al., 1998; Weuve, Barnes, et al., 2018). In fact, Rajabli et al. (2018) found the ancestry-specific region surrounding inheritance of the APOE gene is contributing to lower risk of AD in African American populations; in other words, individuals who inherited the APOE-e4 allele from African ancestors, rather than European ancestors, may be at lower risk for developing AD. On the other hand, other studies found increased risk for the development of AD (Hendrie et al., 2014; Reitz et al., 2013). Regardless, the APOE-e4 allele has been associated with faster cognitive decline in European Americans (-0.037 z-score units/year) compared to African Americans (-0.023 z-score units/year) (Dhana et al., 2022) and adherence to a healthy lifestyle is associated with slower decline in both racial groups (Dhana et al., 2022).

Overall, the literature is clear that if an individual possesses one of the three primary genetic mutations (APP, PS1, PS2) consistent with AD, they will develop AD at an earlier age. In contrast, when examining genetic risk factors associated with LO-SAD, AD predictability is less clear. Specifically, although there have been numerous AD-risk genes identified, possessing a risk gene does not ascertain an individual will develop AD later in life. Therefore, research has

focused on understanding the role of AD-risk genes, and more specifically, how AD-risk genes alter the benefits/consequences of modifiable risk factors.

3.3 Sex

Sex is an additional nonmodifiable risk factor for AD. Overall, the prevalence of AD is greater in women (Brookmeyer et al., 1998). In fact, women account for nearly two-thirds of AD patients (Hebert et al., 2013). Originally, this difference in AD prevalence between women and men was attributed to lifespan duration, as AD incidence rates are comparable across sex (Barnes et al., 2003); however, with additional research, this theory became outdated. To understand this, it is important to consider the developmental and physiological differences between men and women, and how these differences may increase risk for developing different neurological conditions and diseases, which Cahill (2006) argued has not been addressed. Some research suggests that women have higher incidents of AD in old age, but disease progression in men is more accelerated compared to women (Lapane et al., 2001). In contrast, a more recent study suggests that women with higher signals on ^{18}F -Flortaucipir (FTP) PET, which measures the density and distribution of tau neurofibrillary tangles, are more likely to have faster cognitive decline (Buckley et al., 2020). Additionally, women with AD demonstrate greater severity in cognitive impairment compared to men (Irvine et al., 2012).

The interaction between sex and genetic factors is important to consider when characterizing AD risk. The relationship between sex and APOE status is particularly important due to sex differences when characterizing APOE status. Women who carry one APOE-e4 allele have an earlier onset of up to 5 years compared to men (Noguchi et al., 1993). Furthermore, women with two e4 alleles have an earlier onset up to 10 years compared to men (Noguchi et al., 1993). On the other hand, men who have two copies of the APOE-e4 allele (i.e., homozygous)

are at greater risk for cognitive impairment and AD compared to women (see Riedel et al., 2016 for full review). It is also seen that women are more likely (due to APOE-e4 effects) to convert from cognitively normal to mild cognitive impairment (MCI), and from MCI to AD (Altmann et al., 2014; Lin et al., 2015).

Regarding neuropathology, a recent study suggests female APOE-e4 carriers had higher metabolic uptake (as measured by standardized uptake value ratios (SUVr)) in the lateral occipital lobe, even in a group of clinically normal females (Buckley et al., 2020). Research has also examined the potential mediating effect of sex on neuropathological changes and cognitive decline using data from the Harvard Aging Brain Study and Alzheimer's Disease Neuroimaging Initiative (ADNI) (Buckley et al., 2020). Results indicated that women from the ADNI had slightly higher SUVrs on amyloid-beta PET compared to men and were predominantly localized to the temporal lobe. Women also had greater FTP SUVrs in many temporal and extratemporal regions. Overall, this finding suggests women may be more vulnerable to tau neurofibrillary tangles that extends beyond the medial temporal lobe and significantly contributes to risk of faster cognitive decline (Buckley et al., 2020).

3.4 Modifiable risk factors

There has been extensive research examining the associated risk of age, sex, and genetics in the development of AD, and although it is important to understand the unique risk associated with each of these factors, these factors cannot be changed. Modifiable risk factors, or risk that can be changed or modified, provide the opportunity to attenuate risk. As mentioned previously, modifiable risk factors can include physical inactivity, smoking and alcohol use, along with poor sleep, and nutrition (WHO, 2019). Review of all modifiable risk factors is outside the scope of the current dissertation. Chapter 4 (*Nutritional Components and Diet Adherence as a Modifiable*

Risk Factor for Alzheimer's Disease) will discuss the role of nutritional components and diet adherence as it pertains to AD risk.

CHAPTER 4

NUTRITIONAL COMPONENTS AND DIET ADHERENCE AS MODIFIABLE RISK FACTORS FOR ALZHEIMER'S DISEASE

4.1 Diet and Nutrition

Cardiovascular risk factors significantly increase risk for AD and VaD, and as such, modifiable risk factors like diet and exercise may arguably be crucial for maintaining and protecting brain health (Cole et al., 2010). It is no surprise following a healthy diet has the potential for reducing or preventing certain physical health conditions, such as hypercholesterolemia, diabetes, and hypertension (Arnett et al., 2019). However, there are many unanswered questions about the relationship between nutrition, cognition, and brain health. Overall, nutrition has been examined in primarily two different ways: (1) isolate and assess the role of specific dietary components (e.g., micronutrients, dietary fatty acids, carbohydrates); or (2) assess whole diet (e.g., western diet (WD), ketogenic diet (KD), Dietary Approaches to Stop Hypertension (DASH), Mediterranean diet (MD), and Mediterranean-DASH diet Interventions for Neurological Delay (MIND)). The following sections will discuss the literature examining both methods as it pertains to nutrition, physical health, and cognition.

4.2 Micronutrients

Micronutrients, such as vitamins and antioxidants, moderate brain deterioration and assist with maintaining the brain's functional and structural integrity (Dror et al., 2014; Solfrizzi et al., 2017). For example, antioxidants such as Vitamin E and C, carotenoids, and flavonoids, are associated with reduced free radical mediated damage and reduced amyloid-beta toxicity in AD patients via in vitro studies (Feng & Wang, 2012). Overall, research assessing micronutrients as

a dietary component suggests beneficial effects on brain health and will be discussed in greater detail in the following subsections.

4.2.1 Vitamin E

Vitamin E is commonly found in oils (e.g., olive oil, wheat germ oil, safflower oil, sunflower oil (Roman et al., 2019), nuts, and whole grains (Yamada et al., 1999)). Overall, Vitamin E consumption appears to slow the effects of aging (Solfrizzi et al., 2017). Research suggests that Vitamin E assists with regulation of cell proliferation and improving glucose transport/insulin sensitivity (Yu et al., 1998). Regarding cognition, research is inconsistent. Overall, nutritional epidemiological surveys show there is an association between consumption of Vitamin E and delay of cognitive decline/lower risk of AD (Morris, Evans, Tangney, et al., 2005; Wengreen et al., 2007). Additionally, results from the HANDLS study suggest Vitamin E is positively associated with performance on memory and verbal fluency measures (Beydoun et al., 2015). However, controlled clinical trials have yet to find evidence that suggests Vitamin E supplementation significantly influences cognition (Vogel et al., 2000).

4.2.2 B Vitamins

The B vitamins, Vitamin B6, Vitamin B12, and folate, are other important micronutrients when examining brain health. B vitamins are commonly found in the MD. Research indicates deficiencies in these three micronutrients contribute to elevated homocysteine concentrations. Homocysteine is an amino acid that is associated with increased risk of cognitive deficits and decline (Elias et al., 2006), potentially due to cell neurotoxicity (Kruman et al., 2000; Lipton et al., 1997). Disruption in the homocysteine cycle can not only lead to elevated levels, but also contribute to dementia pathology (Clarke et al., 1998). Increased homocysteine has been linked

to early temporal lobe changes and decreased hippocampal width (Williams et al., 2002). Furthermore, it has been hypothesized high homocysteine may contribute to AD by inducing vascular changes (e.g., oxidative stress, contributing to the cholinergic deficit) (Ho et al., 2002; Snowden et al., 1997). Specifically, hyperhomocysteinemia promotes oxidative stress in vascular cells and tissues, along with stimulating generation of ROS (Papatheodorou & Weiss, 2007; Signorello et al., 2002; Weiss, 2005). As summarized by Papatheodorou and Weiss (2007), ROS causes endothelial injury, dysfunction (Tawakol et al., 1997; Weiss, 2005), and activation which results in proinflammatory responses. Deficits in folate and B12 also promote amyloid-beta and tau communication, along with neuronal cell death, all of which have direct effects on cognitive decline (Solfrizzi et al., 2017). In contrast, higher folate, Vitamin B6, and Vitamin B12 have been associated with better cognitive performance (Elias et al., 2006).

4.2.3 Vitamin D

The main function of vitamin D is maintaining calcium, phosphorus, and bone homeostasis (Christakos et al., 2016). As summarized by Solfrizzi et al. (2017), Vitamin D also supports muscle function, cardiovascular health, and reduces risk for diabetes, cancer, and cognitive dysfunction. There are a number of neuroprotective mechanisms associated with Vitamin D. Specifically, it modulates nerve growth production, neurotrophin, glial cell derived neurotrophic factor, NO synthase (important for cellular signaling), and choline acetyltransferase (important for acetylcholine synthesis) (Balion et al., 2012), along with amyloid-beta clearance (Lu'o'ng & Nguyen, 2011). Studies examining the results of consuming higher levels of Vitamin D suggest an association with lower amyloid-beta load in AD brain regions, whereas lower levels of Vitamin D are associated with greater cognitive decline over a 4-year period with

greater risk for AD and all-cause dementia (Mosconi et al., 2014). Overall, Vitamin D deficiency is considered a key factor contributing to dementia incidence rates (Killin et al., 2016).

4.2.4 Flavonoids, Polyphenols, and Carotenoids

Polyphenols, flavonoids, and carotenoids are additional micronutrients worth considering. Polyphenols are a large group of bioactive phytochemicals that include multiple subclasses, including flavonoids (Manach, Williamson, et al., 2005), and they may have important health benefits, protecting against NCDs (Hollman et al., 2010; Hooper et al., 2008; Shen et al., 2012). One of the most studied groups of polyphenols is flavonoids, which also can be divided into subgroups (e.g., flavanols, flavones, etc.). There are more than 8000 polyphenols of plant origin, including 4000 flavonoids (Bravo, 1998; Guasch-Ferre et al., 2017; Pandey & Rizvi, 2009). They are commonly found in fruits, vegetables, and whole grains. For example, common sources are apples, strawberries, blueberries (Schell et al., 2019), chocolate and cocoa (Marika et al., 2019; Schell et al., 2019), coffee, grapes, legumes, nuts, olive oil, oranges, tea (Farzaei et al., 2019), and wine (Roman et al., 2019). Given the relationship between polyphenols and flavonoids, it is not surprising that polyphenols also have antioxidant and anti-inflammatory effects (Maleki et al., 2019). They also assist with cell signaling, gene expression, and have antithrombotic effects on platelets, endothelial cells, NO, vascular smooth muscle cells, monocytes, macrophages, and LDL cholesterol (Huxley & Neil, 2003; Kaliora et al., 2006; Manach, Mazur, et al., 2005).

Regarding AD, polyphenols enhance clearance of A β ₄₂ which results in the inhibition of toxic amyloid-beta clustering (Ayaz et al., 2019). Additionally, polyphenols modulate the tau hyperphosphorylation and prevent tau B-sheet formulation (Zheng et al., 2019), impairing cell integrity and structure. A population-based study that included older adults without dementia

indicated high urinary concentrations of polyphenols was associated with a 47% risk reduction of global cognitive decline and 48% risk reduction in attention functions over three years (Rabassa et al., 2015). In mice, polyphenol consumption has been associated with a reduction in brain lesions due to atherosclerosis (Kaliora et al., 2006; Manach, Mazur, et al., 2005), suggesting that polyphenols have vascular health benefits.

Most polyphenols in the diet are flavonoids (Guasch-Ferre et al., 2017). Flavonoids are naturally occurring in fruits, vegetables, and certain beverages (e.g., tea and wine) (Panche et al., 2016). In fact, there are approximately 6000 flavonoids that contribute to the colorful pigments seen in fruits and vegetables. Depending on the type of flavonoid, they can be commonly found in onions, broccoli, tomatoes, kale, celery, grapes, apples parsley, celery, citrus fruits, and berries (Roman et al., 2019). In addition to their antioxidant effects, flavonoids appear to also possess anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties (Panche et al., 2016). For example, flavonoids are oxidized by radicals resulting in more stable radicals; therefore, they can prevent injury caused by free radicals reducing oxidative stress and damage (Panche et al., 2016). Free radical and ROS are produced when the body metabolizes oxygen or when there is external damage, and the body is continually threatened by them (de Groot, 1994; Grace, 1994) because, as summarized previously, they interfere with cellular functions and lead to cellular damage (Panche et al., 2016). Oxidative stress resulting from cellular damage is related to the onset of a number of health conditions including diabetes, cancer, cardiovascular disease, neurodegenerative disorders and age-related changes (Panche et al., 2016). In fact, consumption of a flavonoid-rich diet is associated with reduced risk for cardiovascular disease and hypertension (Panche et al., 2016).

In addition to reducing cardiovascular disease and hypertension, flavonoid consumption has been linked with biochemical effects including upregulation of antioxidant defenses, assistance with controlling neuronal survival and death, promote angiogenesis and neurogenesis, along with differentiation in mitochondrial interactions, gene expression, and long-term potentiation (Spencer et al., 2009). These biochemical effects are associated with reduced risk of many diseases, including AD and atherosclerosis, and furthermore, flavonoids have beneficial impacts on the CNS and also increase CBF (Jager & Saaby, 2011). Regarding AD, not only do flavonoids reduced vascular disease-related risk, but research also indicates flavonoids may be important for inhibiting certain enzymes that have been linked to certain neurodegenerative conditions (e.g., calcium ions (Ca²⁺) (Panche et al., 2016). Extensive research has focused on the therapeutic modality of flavonoids in treatment of AD. Mechanistically, some research indicates flavonoids may be a significant inhibitor of acetylcholine (Panche et al., 2016). Due to their benefits on the CNS, research emphasizes the importance of dietary flavonoids in therapeutic interventions for AD (Jager & Saaby, 2011). Such therapies have been associated with increased CBF and protection against neuroinflammation leading to neuronal injury and therefore, have been identified as a functional diet treatment for AD (Jager & Saaby, 2011)

Carotenoids are plant pigments, including yellow, orange, dark green, and red (Power, 2019). They are commonly found in foods such as sweet potatoes, carrots, dark leafy greens, avocados, egg yolks, and tomatoes (Tan & Norhaizan, 2019). They are not inherently produced by the human body, and therefore need to be ingested (Zimmer & Hammond, 2007). Carotenoids are also considered to have antioxidant properties that prevent the formation and propagation of free radicals (Gaschler & Stockwell, 2017). In fact, Rubin et al. (2017) demonstrated carotenoids were inversely related to inflammatory markers, including interleukin, in human and animal

models following a 26-day supplementation. Therefore, carotenoids may prevent certain diseases induced by oxidative stress, such as cardiovascular disease (Thies et al., 2017).

In addition to antioxidant effects, research indicates carotenoid consumption may limit neuronal damage via anti-inflammatory properties (Tan & Norhaizan, 2019). It has been suggested carotenoids suppress proinflammatory cytokines (Hadad & Levy, 2017), reduce oxidative stress, and trigger peptide production (Lin et al., 2017). For example, higher levels of beta-carotene consumption have been positively associated with cortical thickness in the dorsolateral prefrontal and temporal poles (Staubo et al., 2017). In fact, beta-carotene is a suggested antagonist to AD (Tan & Norhaizan, 2019). The National Health and Nutrition Examination survey, including 2796 participants over the age of 60, revealed carotenoid supplementation may prevent cognitive decline (Christensen et al., 2020). Another study indicated adhering to a carotenoid rich dietary pattern correlated with a composite score of cognitive functioning at a 13-year follow up (Kesse-Guyot et al., 2014). Correlated domains included episodic memory, semantic fluency, working memory, and executive functioning (Kesse-Guyot et al., 2014). Overall, findings suggest benefits of consuming a diet high in carotenoids, possibly as an intervention, for reducing risk of dementia (Power et al., 2019)

4.3 Macronutrients: Dietary Fatty Acids

Dietary fatty acids (DFA) play an important role in physical and brain function. In general, DFA are separated into 4 main categories: polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), saturated fatty acids (SFAs), and trans fatty acids (TFs).

4.3.1 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) improve activity of brain cells, enhance memory and thinking, and help reduce the risk for cardiovascular and cerebrovascular disease (Farquharson et al., 1992; Innis, 2008; Oken et al., 2008). There are two categories of PUFAs: (1) omega-6 PUFAs, which are commonly found in vegetables and vegetable oils, and includes linoleic acid (LA); and (2) omega-3 PUFAs, which is commonly found in plants fish, and shellfish, and includes alpha-linolenic acid (ALA), eicosatetraenoic acid (EPA), and docosahexaenoic acid (DHA) (Nettleton et al., 2016). Researchers hypothesize PUFAs have vascular, anti-inflammatory, and neuroprotective mechanisms (Belkouch et al., 2016; Cunnane et al., 2009; Latour et al., 2013). In fact, consuming a daily fish oil supplement with anti-inflammatory EPA can initiate a 14% reduction on markers of inflammation (Kiecolt-Glaser et al., 2011). They assist with ensuring brain membrane stability, controlling gene expression, assisting with neurotransmitter release, and contributing to signal transduction and reception (Cole et al., 2009; Salem et al., 2015).

The benefits of PUFAs are clear, but unfortunately, there is not enough available in traditional food sources that also satisfy nutritional requirements (Tocher, 2015). Additionally, diets that include LA and omega-6 fatty acids inhibit the metabolic formation of omega-3s and can possibly lead to deficits in EPA (Roman et al., 2019). Therefore, the ratio of omega-6 and omega-3s may be what is most important in order to reap the full benefits of consumption. Moreover, a balanced intake of omega-3s and omega-6s helps avoid a constant neuroinflammatory state by maintaining homeostasis (Solfrizzi et al., 2017). An unbalanced ratio can cause the arachidonic acid pathway to be increasingly activated, which can in turn increase vascular risk and inflammation (Wendell et al., 2014).

The highest levels of DHA in the human body are in the brain and the retina (Roman et al., 2019). In AD, the presence of DHA in phospholipids in the frontal cortex is reduced (Morris, 2006; Soderberg et al., 1991). This reduction is likely attributable to several different factors, one of which includes predominant omega-6 fatty acid consumption intake during life. Furthermore, clinical studies of DHA and EPA supplementation lead to improvements in cognition in MCI, but not in AD (Ajith, 2018; Yurko-Mauro, 2010). This finding suggests omega-3 PUFAs may serve as a method for preventing cognitive decline. The preventative benefits may occur as early as midlife (Assmann et al., 2018). In fact, a recent 2018 study with randomization revealed long-term nutritional doses of general omega-3s PUFA, specifically ALA, was associated with better cognitive functioning among all supplemented participants (Assmann et al., 2018). This study also found total PUFAs and omega-6 PUFAs were positively associated with overall cognition.

Although research suggests an association between PUFAs consumption and cognition, there are some studies that contradict these findings. Reviews summarizing the effect of supplementation on cognitive performance revealed no beneficial effects on cognition in healthy adults (Sydenham et al., 2012) and in elderly populations (Jiao et al., 2014). The lack of findings in some studies is curious but may be accounted for by a dose-response relationship and/or differential effects among certain populations. For example, a meta-analysis of prospective observational studies indicated seafood and DHA from marine sources were related to a lower risk of dementia; however, this relationship was curvilinear, suggesting PUFAs may be beneficial, but only up to a certain point (Zhang et al., 2016). Additionally, some research indicates differential effects depending on APOE-e4 status. Oleson et al. (2020) discovered that greater PUFA intake was associated with better memory performance in healthy middle-aged adults, but only in those who were carriers of APOE-e4 allele.

4.3.2 Monounsaturated Fatty Acids

Monounsaturated fatty acids (MUFAs) are another type of DFA that may have important implications for brain health. MUFAs are commonly found in vegetable oils (e.g., olive oil, high-oleic safflower and sunflower oil, and canola oil), nuts (e.g., macadamia, hazelnuts, and pecans), fruit (avocados), and animal products high in fat (e.g., ground beef, pork, bacon) (Mashek & Wu, 2015). Consumption of MUFAs and PUFAs has been associated with reduced risk of coronary artery disease (Li et al., 2015). Although MUFAs are found in both animal and plant sources, MUFAs often coexist with SFAs in many foods, especially in animal products (USDA, 2010). Therefore, the research examining MUFAs, and associated health benefits, is mixed, primarily due to the high rate of coexistence with SFAs. For example, in some cases, MUFAs may be positively associated with the progression of coronary heart disease when people are consuming large amounts of both MUFA and SFA (Ros, 2003). When interpreting research, it is clearly important to consider that MUFAs and SFAs coexist in many foods, which can make characterizing the relationship to cognition and other health benefits difficult. It is also important to consider the number of bonds when determining the benefits of MUFAs. Fatty acids with a double bond (*trans*) promote higher levels of LDL cholesterol and lower levels of high-density lipoprotein (HDL) cholesterol; however, this consideration is not just for MUFAs but for all DFAs, more generally (Brouwer et al., 2010; Watts et al., 1996). Regarding MUFAs more specifically, *trans* MUFAs are more commonly found in the WD, beef, and dairy products (Degirolamo & Rudel, 2010), which are known to have high levels of SFAs.

Regarding cognition, there is some evidence to suggest consumption of MUFAs may be beneficial for brain health. In fact, MUFA-enriched diets, such as the MD, have been suggested to delay age-related cognitive decline and reduce risk for developing AD (Morris & Tangney,

2014). Important to note, however, many MUFAs that have been shown to improve brain health or reduce risk for cognitive decline are also likely to be high in PUFAs and plant based. For example, nuts and olive oil are both rich in PUFAs and MUFAs, and research indicates nut intake is associated with better cognition in older age (Solfrizzi et al., 2017). Extra virgin olive oil is high in both PUFAs and MUFAs and has been researched extensively in the literature. Specifically, studies suggest extra virgin olive oil may serve a protective role against the development of AD, as shown in MD clinical trials and population studies (Casamenti & Stefani, 2017).

Overall, the literature is mixed regarding the benefits of MUFA consumption. Research examining plant based MUFAs paired with PUFAs, seem to have beneficial effects, suggesting that when unpaired with SFA, MUFAs have positive benefits on brain health.

4.3.3 Saturated Fatty Acids

The benefits of saturated fatty acids (SFAs) are even more controversial, compared to PUFA and MUFA consumption. SFAs are natural fats, and it is impossible to consume unsaturated fat without SFAs (Harcombe, 2019). As summarized by de Souza et al. (2015), main sources of SFA include animal products (e.g., butter, cow milk, meat, salmon, egg yolks), plant products (e.g., chocolate, cocoa butter, coconut, and palm oils) and processed foods. Overall, SFAs have been associated with increased vascular risk. For example, research suggests SFAs block LDL receptors, which in turn, increases circulating LDL-cholesterol and total cholesterol in the blood stream (Roman et al., 2019). However, recommendations to reduce saturated fat consumption to reduce risk of cardiovascular disease assumes that reduction in cardiovascular risk will accompany reductions in LDL cholesterol (American Heart Association Nutrition et al., 2006). Interestingly, there is little evidence from clinical trials and epidemiological studies that

reducing saturated fat below 9% of total energy intake per day reduces risk for cardiovascular disease (Dayton & Pearce, 1969; Leren, 1970; Turpeinen et al., 1979). In fact, another study suggests when SFA intake was at 9.5%, lower than the comparison group (12.4%), there were no differences in incidence of coronary heart disease or cardiovascular disease (Howard et al., 2006). A recent review assessing the relationship between dietary SFA and heart disease concluded that findings are mixed (Heileson, 2020). Overall, results from observational studies have not found an association between SFA and heart disease. In contrast, meta-analyses of randomized controlled trials are inconsistent, but overall, there lacks an association between SFA and heart disease.

Some researchers argue SFAs have been convoluted with the harmful effects of processed food. The Dietary Guidelines for Americans (2010), created by the U.S. Department of Agriculture (USDA) and Health and Human Services (HHS), indicated the following foods to be the primary sources of saturated fat: pizza, desserts, candy, potato chips, past, tortillas, burritos, and tacos (USDA & HHS, 2010). In the same regard, the guidelines indicated natural sources of saturated fat include dairy products (e.g., cheese, MILK, butter), nuts, and seeds. Arguably, if more natural foods were consumed, therefore obtaining natural sources of SFA, the negative health benefits previously associated with SFA might decrease due to the additional reduction in sugar and trans fats (Fiolet et al., 2018).

Importantly, there is a body of research indicating diets high in saturated fat that also emphasize overeating contribute to the development of obesity, metabolic syndrome, and type 2 diabetes (Peila et al., 2002), which are known to increase risk for developing dementia. Additionally, saturated fats that are present in the blood stream, often stearic and palmitic acids, are associated with dementia risk (Amadiou et al., 2017; Volk et al., 2014) and high saturated fat

has been associated with impairment in a number of cognitive domains, including attention, working memory, inhibition, and other memory functions (Francis & Stevenson, 2013).

4.3.4 Trans Fatty Acids

Like SFA, trans fatty acids (TFs) are naturally occurring. As summarized by Wanders et al. (2017), TFs are commonly found in foods that originate from animals, such as cows and sheep, and in foods that include partially hydrogenated vegetable oils, such as fried foods and packaged goods. TFs coming from hydrogenated oils, but not animals, have been shown to increase blood cholesterol and risk for coronary heart disease (de Souza et al., 2015). Research suggests higher intake of TF and SFA, while also consuming low amounts of MUFAs and PUFAs can contribute to insulin resistance, among other vascular changes (Lichtenstein & Schwab, 2000).

There is growing evidence TF consumption contributes to AD risk and cognitive decline. In the brain, TF contributes to the integrity of the myelin sheath, which helps insulate neurons and assists with communication among neurons (Ginter & Simko, 2016). Therefore, TF consumption may have implications on neuronal communication, which is important for cognitive functioning. Research suggests diets high in TF may be associated with cognitive decline in older adults (Morris et al., 2004) and that consumption of saturated or TF is significantly associated with incidence of AD (Barnard et al., 2014; Morris & Tangney, 2014). It has been hypothesized the association between TF intake and AD risk is mostly accounted for by the APOE-e4 allele, as it produces a protein that assists in cholesterol transport (Puglielli et al., 2003). As such, foods high in TFs may also be associated with increases in blood cholesterol, which in turn contributes to amyloid-beta production and/or aggregations (Puglielli et al., 2001), especially in those who are APOE-e4 positive. Additionally, Morris (2009) found that

approximately 3.9 years after initial intake, TF consumption was positively correlated with AD risk. In fact, those who had high TF consumption (80%) had four times the level of risk for developing AD. Accompanying AD risk, TF has also been associated with reduced brain volume and poor cognitive performance (Bowman et al., 2012). Even in healthy samples, TF is associated with worse memory performance (Golomb & Bui, 2015). When cross-sectionally examined, for every single gram of TF consumed per day, word recall declined by 0.76 in a healthy population. In contrast, individuals who consumed no TF per day recalled 11-12 more words when compared to individuals that consumed the highest amount of TF per day, which was 15.7 grams per day in the sample (Golomb & Bui, 2015). Furthermore, TF were simultaneously associated with metabolic factors including systolic blood pressure, waist circumference, and body mass index (BMI), which are all likely contributing to oxidative stress in the brain (Golomb & Bui, 2015). Overall, the research is clear that consuming high levels of TFs negatively impacts physical and brain health. In addition, TF consumption is associated with AD risk through various mechanisms, some of which include increasing risk for cardiovascular disease and oxidative stress.

4.4 Carbohydrates and Glucose

Fats, proteins, and carbohydrates are three molecules that provide the brain and body with energy. Glucose is a major source of energy to the brain and is primarily obtained from carbohydrates (Sunram-Lea & Owen, 2017). Simple carbohydrates provide immediate energy, as they are quickly digested (AHA, 2018). These carbohydrates can take the form of simple sugars (i.e., white or refined), or naturally occurring in fruit or milk (AHA, 2018). Although naturally occurring sugars are found in a variety of fruits, the sugars are accompanied by other nutrients (i.e., vitamins and minerals), fiber, and water. As such, naturally occurring sugars should be

consumed over refined sugar. In contrast to simple carbohydrates, complex carbohydrates digest slowly and provide a consistent source of energy (AHA, 2018). Foods that are considered complex carbohydrates include legumes, starchy vegetables, and whole grains (AHA, 2018).

The brain uses glucose for energy; therefore, low energy consumption deprives the brain of necessary energy (Sunram-Lea & Owen, 2017). Although results are somewhat inconsistent, glucose intake has shown to have positive aspects on some domains of cognitive performance, such as verbal memory, working memory, and attention (Smith et al., 2011). Depriving the brain of glucose can result in disruption of neuronal activity and poor cognitive functioning (Holmes et al., 1983). In contrast, providing too much glucose to the brain can lead to damaging effects, such as in the WD (more detail in the *Western Diet* section) which is strongly associated with the development of atherosclerosis, diabetes, hypertension, and hyperlipidemia (Dearborn et al., 2014; Wang et al., 2016), cardiovascular disease, and coronary heart disease (Medina-Remon et al., 2018). Regarding brain functioning more specifically, fruit consumption, for example, has been negatively associated cortical thickness in the inferior parietal, supramarginal, superior parietal, and precuneus cortices (Staubo et al., 2017). Additionally, research also suggests lower temporal and hippocampal volumes associated with high fruit intake (Gu et al., 2015). Although these results may seem unexpected, fruits are considered simple carbohydrates, and most fruits have a relatively high content of simple sugars and high glycemic index; therefore, the negative associations are likely attributable to carbohydrate consumption, as it has been associated with increased risk for MCI (Jacka et al., 2015).

Diets marked by excessive consumption of high glycemic index foods, often characterized by processed carbohydrates and simple sugars, trigger elevated peripheral glucose, insulin resistance, and impaired glucose metabolism (Livesey et al., 2008). Higher carbohydrate

consumption, specifically refined carbohydrates, increases risk for metabolic factors including elevated triglycerides, reduced HDL cholesterol, and increased LDL concentrations (Parks & Hellerstein, 2000; Siri & Krauss, 2005). These metabolic factors are associated with vascular risk, which arguably result in increased dementia risk. Additionally, elevated blood glucose, impaired glucose metabolism, and peripheral hyperglycemia are associated with increased AD risk (Livesey et al., 2008; J. K. Morris et al., 2014). Furthermore, a cross-sectional study of cognitively normal healthy adults revealed significantly higher amyloid burden in people who adhered to a high-glycemic diet and had higher sugar and carbohydrate intake (Taylor et al., 2017). In fact, participants without diabetes at follow-up, as part of the Adult Changes in Thought Study, had higher-than-average glucose levels within the 5 years leading up to the onset of dementia (Crane et al., 2013). Although there is some indication of negative effects on cognition resulting from long-term refined sugar intake, there is still an overall lack of human research and is an important future direction.

In summary, many diet components have been examined as it pertains to reducing risk for AD and NCDs. Overall, research is promising, suggesting some dietary components have benefits on vascular health, reduce neuroinflammation and oxidative stress, and ultimately yield neuroprotective effects. Examining diet components offers unique benefits, including isolating the nutritional information and associated relationships with each component. However, isolating these relationships remains difficult because many diet components naturally occur with other nutrients, which became clear when reviews, clinical trials, and prospective/observational studies yielded mixed results. For example, although there are simple carbohydrates (sugar) in both a tablespoon of white sugar and an apple, the skin of the apple offers other vitamins and minerals, along with fiber that provide additional nutritional benefit. To address this limitation, research

has examined whole diets, to better account for the interaction among nutrients and foods. Whole diets, as it pertains to AD and vascular health, will be discussed in subsequent sections.

4.5 Western Diet

Overall, a healthy diet consists of fruits, vegetables, legumes, nuts, and whole grains, with reduced sugar, salt, SF, and TF (WHO, 2019). The Western Diet (WD) consists of high proportions of fat and refined sugar, along with reduced complex carbohydrate and fiber consumption. Additionally, it is consistent with a general reduction in fruit and vegetable consumption, as summarized by Francis and Stevenson (2013). Notably, highly processed foods are a hallmark of the WD (Zinocker & Lindseth, 2018). As discussed previously, fat consumption (PUFAs and MUFAs) in general does not necessarily result in negative brain health or reduced cognitive abilities; however, high saturated fat and refined sugar increases risk for dementia and vascular risk factors. Foods consistent with the WD include red meat, sausages, steak, and other roast meat (Jacka et al., 2015), refined carbohydrates (i.e., soft drinks, pastries, desserts, and white bread) (Statovci et al., 2017), high fat dairy products, and sugar.

Cellularly, WD adherence is associated with changes in the gut microbiota, which is associated with obesity and metabolic diseases (Martinez et al., 2017), including gut inflammation (Zinocker & Lindseth, 2018). As mentioned previously, WD adherence is strongly associated with the development of atherosclerosis, diabetes, hypertension, and hyperlipidemia (Dearborn et al., 2014; Wang et al., 2016), cardiovascular disease, and coronary heart disease (Medina-Rejon et al., 2018). Together, these diseases interact to cause changes in metabolism, inflammation, and microvascular health: all of which are associated with white matter injury (Dearborn et al., 2014; Wang et al., 2016). Overweightness and obesity are associated with poor

memory performance, due to impairments associated with SFA and sugar consumption, which are consistent with WD adherence (Lopez-Taboada et al., 2020).

Regarding cerebrovascular health and cognition, in addition to white matter injury, research suggest WD dietary habits are associated with reduced hippocampal volume (Jacka et al., 2015), reduced visuospatial abilities (Gardener et al., 2015), and AD (Gustaw-Rothenberg, 2009). Importantly, white matter disease fosters the development and progression of cognitive decline and dementia (Smallwood et al., 2012). Animal studies have reported a significant and positive relationship between high fat/high cholesterol diets to AD biomarkers, including amyloid-beta levels, gliosis, and impaired energy metabolism (Levin-Allerhand et al., 2002; Refolo et al., 2000).

4.6 Ketogenic Diet

To combat negative consequences associated with the WD, other diets have been proposed and examined. As summarized by Hallbook et al. (2012), the ketogenic diet (KD) is characterized by a ratio of high fat, moderate protein, and low carbohydrate consumption. It was first examined in epileptic populations and is now an effective intervention for treatment of refractory epilepsy. More recently, mechanisms of the KD for reducing or preventing dementia have been inspected. In general, when fat consumption is increased and carbohydrate consumption is simultaneously reduced, glycolysis is reduced, which forces the liver to oxidize fatty acids and transform them into ketone bodies (Kossoff et al., 2009). Once the ketone bodies are released from the liver, they act as an alternate energy source to the brain (other than glucose), providing neuronal energy and fulfilling the oxidative needs of neurons (Chowdhury, Jiang, Rothman, & Behar, 2014). Continuing to consume a diet of the appropriate ratio (fat:protein:carbohydrate) will ensure the body remains in a state of ketosis. Aging is associated

with reduced ability to metabolize glucose in the brain and this reduction appears to be more pronounced in individuals who carry the APOE-e4 allele (Reiman et al., 2005). When glucose is limited due to reduced energy consumption, there are complications with glucose transport, or mitochondrial function is impaired, such as in AD, ketone bodies provide a sufficient energy source for the brain (Ulamek-Kozioł et al., 2019).

KD has several notable physical health benefits. In fact, adhering to a low calorie KD is associated with reduced BMI, waist circumference, HbA1c, total cholesterol, triglycerides, systolic and diastolic blood pressure, and indicators of liver damage and disease in obese and overweight individuals (Castellana et al., 2020). Although there appears to be some health benefits beyond weight loss, KD adherence has also been associated with increases in HDL-C and LDL-C (Bueno et al., 2013), which raises concern about the diet sustainability. In fact, one study that included healthy, normal weight volunteers demonstrated a 44% increase in serum LDL-C and 30% reduction of the LDL-C receptor following a 3-week KD (Retterstol et al., 2018). It is possible, however, that perceived negative health consequences are not well understood. For example, in a sample of children with epilepsy, increases in blood lipid levels were only observed initially, before declining and eventually returning to baseline levels (Kapetanakis et al., 2014).

Ketone uptake does not appear to be impaired in AD (Cunnane et al., 2016). The preclinical stages of AD, which are suspected to persist for decades before the onset of symptoms, are consistent with glucose hypometabolism, whereas the onset of AD pathology is consistent with impairment of glucose uptake (Hertz et al., 2015). Additionally, AD is associated with the inability to transport glucose, impaired glycolysis, and mitochondrial dysfunction (Hertz et al., 2015). A review by Ingram et al. (2006) identified benefits associated with caloric

restriction, which is also consistent with the KD, including improved mitochondrial function, reduced inflammation, and improved activation of neurotrophic factors. Importantly, there are only a few interventional studies in animals and humans that clearly address the relationship between KD adherence and risk for AD. In mice models, there are associated improvements in cognition following KD adherence. Suspected mechanisms include modified neurotransmitter transport and synaptic maintenance, along with improvements in abnormal features, such as amyloid-beta accumulation or neuroinflammation (Lilamand et al., 2020). Limited results from human intervention studies suggest improved cognition with KD adherence in the domains of memory, executive function, and global cognitive domains, regardless of initial impairment prior to beginning the KD (Lilamand et al., 2020).

4.7 Dietary Approaches to Stop Hypertension

Originally developed to address hypertension, the Dietary Approaches to Stop Hypertension (DASH) diet emphasizes high intake of fruits and vegetables; moderate consumption of low-fat dairy products, poultry, and fish; considerable amounts of plant protein from legumes and nuts; and low consumption of red meat, sugary beverages, sweets, and sodium (Medina-Remon et al., 2018). The goal of the DASH diet is to reduce dietary total fat, SF, and dietary cholesterol, while increasing potassium, calcium, magnesium, fiber, and protein (Medina-Remon et al., 2018). Studies suggest adherence to the DASH diet has physical health benefits associated with blood pressure reduction. A review by Medina-Remon et al. (2018) suggests the DASH diet promotes weight loss and maintenance, reduced risk for cardiovascular disease, and prevents the appearance of type 2 diabetes while improving insulin sensitivity. Furthermore, DASH diet adherence resulted in significant reductions in LDL cholesterol, HDL cholesterol, apolipoprotein A-I protein, intermediate-density lipoprotein and large LDL particles, and LDL

peak diameter compared to controls in a randomized controlled trial (Chiu et al., 2016). Not surprisingly, when partnered with exercise and additional life changes, individuals can achieve greater weight loss and blood pressure reductions in combination with DASH diet adherence (Blumenthal et al., 2010).

In addition to cardiovascular benefits, the impacts of DASH diet adherence on brain health have been examined. Combined with a behavioral weight management program, individuals adhering to a DASH diet in a four-month clinical trial showed greater improvements in executive functioning, memory, learning, and psychomotor speed. Those who received just the diet intervention displayed better psychomotor speed compared to controls (Smith et al., 2010). Additional research indicates the DASH diet is associated with reduced and slower rates of cognitive decline (Medina-Remon et al., 2018). However, a prospective study examining the risk of AD, following a DASH diet, found only modest effects (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015). Although there is some research examining the cognitive and brain health benefits with DASH diet adherence, a recent review from 2019 determined there was only one cross-sectional study (Blumenthal et al., 2017), one randomized clinical trial (Smith et al., 2010), and six longitudinal studies examining the relationship between DASH diet, cognition, dementia, and/or AD (van den Brink et al., 2019). Cross-sectional data indicate DASH diet adherence is associated with verbal memory function, but not with visual memory, executive functioning, or processing speed (Blumenthal et al., 2017). Longitudinal studies indicate high DASH diet adherence is associated with up to 28% reduced risk for MCI, along with less changes in cognition, episodic memory, and semantic memory (van den Brink et al., 2019). Furthermore, adherence to a DASH diet was associated with better than average cognition in adults at four-year follow up; however, some studies have failed to find beneficial effects on cognitive decline

(van den Brink et al., 2019). Overall, there appears to be a need for additional research to better understand the relationship between DASH diet, cognition, and AD risk. Notably, the literature that currently exists does suggest potential reduced risk for MCI and cognitive decline with DASH diet adherence, along with cognitive benefits.

4.8 Mediterranean Diet

Like the DASH diet, the Mediterranean diet (MD) demonstrates protection against cardiovascular risk factors and other adverse health conditions. Although similar, there are notable differences between the DASH and the MD. First the DASH diet is characterized by lower consumption of SF and commercial pastries and sweets, and second, the DASH diet allows for greater dairy intake compared to the MD (Solfrizzi et al., 2017). The MD is defined using the traditional dietary pattern found in Greece, southern Italy, Spain, and other olive-growing countries (Willett et al., 1995). It emphasizes high consumption of plant-based foods (e.g., vegetables, fruits, legumes, and cereal) and olive oil, relying exclusively on olive oil as the primary fat source. Additionally, the MD emphasized high-moderate fish consumption, moderate-low dairy consumption; low meat and poultry consumption; and low wine consumption (Solfrizzi et al., 2017). The recommended foods tend to be rich in antioxidants such as Vitamin E, C, B12, folate, carotenoids, MUFAs, PUFAs (Gomez-Pinilla, 2008), polyphenols, Vitamin K, lutein, and omega-3 fatty acids (Kastorini et al., 2011; Morris et al., 2002; Morris, Evans, Bienias, et al., 2005). Important to consider is that the early Mediterranean dietary pattern examined in epidemiological research (high intake of olive oil, reduced intake of meat and dairy, increased consumption of green leafy vegetables and fruit) is not consistent with the current dietary pattern in Mediterranean regions; rather, Mediterranean populations currently consume dairy and meat products (de Lorgeril & Salen, 2008), inconsistent with the early MD pattern.

MD adherence can reduce risk for obesity and overweightness, lower abdominal adiposity, protect against the development of diabetes, coronary heart disease (Medina-Remon et al., 2018), and reduce blood pressure and cholesterol (Domenech et al., 2014). Research suggests MD adherence may also have positive impacts on brain structure and protect vascular pathways. For example, MD was associated with preserved microstructure white matter in numerous brain regions and a 10-year delay in cognitive aging (Pelletier et al., 2015). Results further suggest high adherence to the MD is positively associated with cortical thickness in areas that degenerate with onset of AD (Staubo et al., 2017). It has been suggested structural changes may occur as early as middle age, with greater cortical thickness in the posterior cingulate cortex following MD adherence (Mosconi et al., 2018).

Regarding cognition and AD risk more specifically, Singh et al. (2014) conducted a systematic review and meta-analysis to characterize the association between MD and cognitive impairment. Overall, results suggest higher MD adherence was associated with reduced risk of MCI and AD. Participants who were in the highest MD percentile had 33% less risk for cognitive impairment, both MCI and AD, compared to the lowest MD percentile. Even amongst cognitively normal participants, higher MD adherence was still associated with reduced risk for MCI and AD.

Since the 2014 review, additional research has examined the relationship between MD, cognition, dementia, and/or AD. Based on a recent review from 2019, the MD has been examined in relation to cognitive function, dementia, and/or AD in 12 cross-sectional studies, 1 case control study, 31 longitudinal studies, and 3 randomized controlled studies (van den Brink et al., 2019). Cross-sectional findings are somewhat inconsistent, however. Some findings indicate the MD was associated with better cognitive functioning in domains of global cognition,

language, memory, executive functioning, and verbal ability. Additionally, these cognitive benefits were in middle-age populations, suggesting the benefit of diet and cognition may occur earlier in life. In contrast, some cross-sectional findings failed to find an association between MD and cognitive functioning (van den Brink et al., 2019). Overall results from longitudinal studies suggest reduced risk for cognitive decline with higher MD adherence and an 8% lower risk of mild cognitive impairment (van den Brink et al., 2019). In fact, a more recent longitudinal study noted cognitive benefits over a five-year period of MD adherence and found that MD adherence was significantly associated with lower AD risk at follow-up (Wade et al., 2019). Furthermore, highest MD adherence was associated with 40-54% lower AD risk and this risk reduction increased to 73% in older adults (van den Brink et al., 2019). Lastly, the recent review also covered randomized controlled trials assessing benefits of MD adherence (van den Brink et al., 2019) and results suggest benefits in executive function, memory, processing speed, and visual spatial memory.

The MD, especially when supplemented with extra virgin olive oil, has not only been associated with better cognitive performance, but also reduced risk of developing MCI (van den Brink et al., 2019). Patients with diagnosed AD enrolled in a randomized controlled trial who adhered to a coconut oil enriched MD demonstrated improvements in episodic, temporal orientation, and semantic memory (de la Rubia Orti et al., 2018). This effect was more evident in women who in the were mild-moderate AD state at baseline and men in the severe AD state at baseline (de la Rubia Orti et al., 2018), which further suggests that dietary benefits may affect groups differently (e.g., sex, APOE status).

Overall, the MD reduces vascular risk factors, protects against effects of oxidative stress, and reduces neuroinflammation. Hypothesized mechanisms include metabolic, oxidative, and

inflammatory properties. Among the food and nutrients that characterize the MD (MUFAs, omega-3 PUFAs, flavonoids, and vitamins), they have been associated with lower inflammatory and oxidative load properties that reduce cardiometabolic risk factors, along with cognitive decline and dementia (Frisardi et al., 2010). Furthermore, it has been proposed these properties may begin protecting the brain in both preclinical dementia and after the onset of symptoms, suggesting the MD acts on cognition through cerebrovascular means (Solfrizzi et al., 2011).

4.9 Mediterranean-DASH Diet Intervention for Neurological Delay

A hybrid between the DASH and MD, the MIND diet emphasizes dietary components that are associated with neuroprotection and reduced dementia risk. There are 10 food groups in the MIND diet that significantly contribute to brain health, as summarized by Solfrizzi et al. (2017), which include the following: green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine. Additionally, the MIND diet has characterized five unhealthy food groups: red meats, butter and stick margarine, cheese, pastries, sweets, and fried/fast food. Uniquely, the MIND diet specifies berry and green leafy vegetable consumption, but does not specify high fruit consumption, potato, or the number of fish meals per week, all of which are previously outlined in either the DASH/MD.

Although the DASH, MD, and MIND share protective mechanisms against physical, cardiovascular, and cerebrovascular conditions, MIND diet adherence appears to be more predictive of cognitive decline compared to DASH and MD alone (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015). Cross-sectionally, MIND diet adherence is associated with better cognitive performance, with greater adherence associated with greater risk reduction (van den Brink et al., 2019). More specifically, higher MIND diet scores have been associated with slower rates of cognitive decline and 53% AD risk reduction compared to lower MD adherence (35%

risk reduction) (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015). Similarly, a recent longitudinal study suggests that at 12-year follow-up, higher MIND diet adherence was associated with a 19% reduction in developing MCI or dementia, with those at the highest level of adherence experiencing the greatest risk reduction of 53% (Hosking et al., 2019).

MIND diet findings suggest this diet may be more beneficial for the prevention of AD, compared to the DASH and MD, primarily due to research suggesting only the highest adherence of both DASH and MD are associated with prevention (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015). The MIND diet is suspected to improve overall brain health (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015), rather than targeting AD pathology specifically. However, there is currently not enough causal evidence to establish neuroprotective effects, primarily because large population-based studies are still particularly young, between the ages of 60-64 years (Hosking et al., 2019). There is one recent longitudinal study from the Wisconsin Registry for Alzheimer's Prevention (WRAP) that examines the relationship between cognition and MIND diet adherence as a secondary outcome. From baseline ($M_{\text{age}} = 57$) to 6.3-year follow-up, they found no relationship between self-reported health behaviors (e.g., physical activity) and cognitive decline. However, secondary outcomes indicated that MIND diet adherence had a small effect on executive functioning (Mueller et al., 2020); specifically, those with higher scores, indicating greater MIND diet adherence, showed slower decline in executive functioning when compared to those with lower diet adherence. Unfortunately, when other health variables were accounted for, MIND diet consumption only had a weak association with cognitive decline. Mueller and colleagues (2020) conceptualized these findings in three ways: (1) the range of cognitive decline in middle age is too small to observe relationships with health behaviors; (2) the putative associations of health behaviors on cognition may not be robust enough for this age

range; or (3) self-reported measures of health behaviors may not be optimal when predicting cognitive decline.

Although the effect of diet on executive functioning was quite small in the study conducted by Mueller and colleagues (2020), other studies have found larger effects when examining MIND diet adherence and risk for cognitive decline/dementia (M. C. Morris et al., 2014; Morris, Tangney, Wang, Sacks, Bennett, et al., 2015; Solfrizzi et al., 2017). The rate of change in cognition longitudinally within the WRAP sample was estimated at $-.007$. A previous study conducted by Mormino et al. (2017), estimated rate of cognitive change longitudinally to be approximately $-.043$ in APOE-e4 carriers. Notably, in the study by Mormino and colleagues (2017), APOE status was not a significant predictor for cognitive decline when amyloid-beta status was accounted for. Interestingly, Mueller and colleagues (2020) failed to find a significant relationship between APOE-e4 status and longitudinal cognition and in fact, the WRAP group has yet to find this association (Johnson et al., 2018). This is surprising given the WRAP is considered an enriched sample for AD family history and APOE-e4 genotype, and APOE-e4 genotype is a well-established risk factor for cognitive decline (Howieson et al., 2003). Authors attribute the lack of significance to a younger aged sample, as most participants at follow-up were considered late middle age. Regardless, this warrants future investigation to clarify this relationship and potentially identify what is unique about the WRAP sample.

There are significant benefits to the WRAP study cohort, including a sample of individuals who have a familial risk for AD and individuals who are declining at a faster rate (Johnson et al., 2018; Kosciak et al., 2019). Furthermore, the recent longitudinal study by Mueller and colleagues (2020) contributes to the limited literature examining the effects of the longitudinal effects of MIND diet on cognition. However, the authors acknowledged a few

limitations that are important to consider for future studies. First, self-reported health behaviors were used as predictors, and did not consider objective measures of health or the overall cardiovascular risk as covariates and/or mediating factors on cognition. Self-reported health behaviors are especially susceptible to under and overreporting. Second, authors took a comprehensive approach to examine health behaviors, which have produced mixed results in previous studies (Sturman et al., 2005). It is possible that taking a comprehensive approach fails to characterize certain relationships, such as the behavioral interaction in individuals who engage in multiple health behaviors. Although there are some longitudinal studies, they are not without limitations that provide future directions for additional research.

CHAPTER 5

THE CURRENT STUDY AND SPECIFIC AIMS

5.1 The Current Study

Of all the diets and nutrient components mentioned, there are key mechanisms that remain relatively consistent. Anti-inflammatory, oxidative stress, vascular, and neuroprotective mechanisms are important for reducing risk for neurodegeneration, and furthermore, cognitive decline and dementia. Importantly, some of the changes associated with the aforementioned modifiable risk factors can begin as early as midlife (Sperling et al., 2011), which suggests associated vascular health changes (e.g., hypertension, hypercholesterolemia, obesity) also potentially begin before or during midlife. For example, midlife obesity poses greater risk for development of dementia later in life, compared to late-life obesity (Ahmed et al., 2019). The cumulative exposure to cardiovascular risk factors from early to mid-adulthood is associated with worsening cognition in mid-life (Yaffe et al., 2014). Therefore, brain changes associated with the AD process are occurring decades prior to the onset of symptoms (Sperling et al., 2011). It is unlikely that a single risk factor solely contributes to the development of neurodegenerative diseases and rather, improving all risk factors may have similar health benefits, such as improvement in vascular health. For example, vascular cognitive impairment, which is associated with both AD and VaD, can be minimized by reducing risk for cerebrovascular and cardiovascular dysfunction. Diet is one way to mitigate vascular risk, as well as other risk factors (e.g., physical health, NCDs, etc.), for neurodegenerative processes. As such, there is increasing evidence that indicates a significant relationship between diet and cognition which will be explored in the current study.

5.2 Aims

The current dissertation aimed to examine the relationship between diet, physical health, and cognition. The general goal of the proposed project was to investigate the longitudinal effects of MIND diet consumption and physical health measures (i.e., waist-to-hip ratio (WHR)) on cognition. The central hypothesis was that diet would have significant associations with cognition, longitudinally, as would physical health. Furthermore, it was expected APOE genotype would moderate the relationship between diet and longitudinal cognitive performance.

The central hypothesis was objectively tested by the following aims:

1. Examine the longitudinal relationship between MIND diet adherence and cognition.

- a. It was hypothesized that participants' MIND diet score (with higher scores indicating higher diet concordance) would be positively associated with cognition at follow-up, as measured by neuropsychological tests, even after accounting for physical health (WHR) and nonmodifiable risk factors (age, gender, APOE genotype). WHR was chosen over other physical health factors because research suggests increases in WHR in middle and older adult age (40-79) has been associated with impaired executive functioning (Zade et al., 2013; Hartanto & Yong, 2018). Furthermore, it is argued to be a better estimate of health, as it considers weight and fat location, where BMI does not. For a detailed review on specific cognitive domains that were hypothesized to be affected by MIND diet, please see the *Materials and Methods* Section.

2. Examine the longitudinal relationship between physical health and cognition.

- a. It was hypothesized that better physical health, as measured by WHR, an objective physical health measure, would be positively associated with cognition

at follow-up, even after accounting for nonmodifiable risk factors. It was further hypothesized that memory (including immediate and delayed) and executive functioning domains would be associated with WHR. For a detailed review on specific cognitive domains that were hypothesized to be affected by WHR, please see the *Materials and Methods* Section.

3. Characterize the longitudinal relationship between APOE genotype and cognition.

Additionally, determine whether APOE genotype moderates the relationship between MIND diet adherence and cognitive health over time.

- a. Despite inconsistent findings in characterizing the relationship between APOE-e4 status and cognition, it was hypothesized that APOE risk would be negatively associated with cognitive health at follow-up in middle-aged adults (45-64 years at baseline), as measured by neuropsychological tests. For a detailed review on specific cognitive domains that were hypothesized to be associated with APOE genotype risk, please see the *Materials and Methods* Section.
- b. Assuming that APOE genotype is a significant predictor for cognitive health at follow-up, it was hypothesized that APOE genotype would moderate the relationship between MIND diet adherence and longitudinal cognitive health. More specifically, those with a higher APOE risk score and who had greater MIND diet adherence, would have greater benefits in cognition (i.e., immediate memory, delayed memory, and executive functioning), longitudinally. Theoretically, those with the APOE-e4 allele may be more susceptible to AD-related neuropathological changes given the predisposition for BBB dysfunction (Montagne et al., 2020) and may differentially benefit from MIND diet adherence.

Based on the literature, individuals who are carriers of the APOE-e4 genotype are already vulnerable to poor amyloid-beta clearance and reduced cholesterol transport. APOE-e4 genotype, however, is not necessarily causative for AD and possessing the e4 allele only increases risk for the development of the disease; it does not guarantee phenotype expression. Considering diet, TF consumption is associated with worse cognitive decline in individuals with the APOE-e4 allele and furthermore, it has been suggested that these individuals experience greater benefit from PUFA supplementation (Oleson et al., 2020), an important dietary component of the MIND diet. In fact, greater consumption of PUFA has been associated with better memory performance in middle-aged adults only in those who were APOE-e4 positive (Oleson et al., 2020). Overall, the goal of this aim was to better clarify the interaction of APOE-e4 genotype and MIND diet on cognitive performance.

CHAPTER 6

MATERIALS & METHODS

The Wisconsin Registry for Alzheimer's Prevention (WRAP) was established in 2001 (Sager et al., 2005), a longitudinal observational study ($n = 1561$) of participants with familial risk for AD enrolled during midlife (baseline $m_{age} = 54$) (Johnson et al., 2018). Major goals of the WRAP study include the following: (1) determine whether AD-related cognitive trajectories can be detected in midlife and distinguished from normal aging using sensitive cognitive assessments; (2) determine the effect of genetic vulnerability on AD-related cognitive trajectories and biomarkers; (3) determine the biomarker patterns associated with cognitive trajectories and the development of symptomatic cognitive dysfunction; (4) examine the influence of health behaviors and risk and resilience to brain pathology and cognitive decline due to AD (Johnson et al., 2018).

6.1 Participants

A subset of the WRAP data was requested and received. Data from the WRAP was uploaded to a sharing portal on February 14, 2022. The initial data freeze included a total of 6,964 participants with cognitive data from at least one study visit. Participants were excluded from analysis if they had a consensus conference diagnosis of *Impaired, Not MCI* ($N = 33$), *Clinical MCI* ($N = 137$), or *Dementia* ($N = 19$).

6.2 Procedure and Measures

Each study visit lasts approximately five hours and at each visit, participants completed a series of in-person assessments and questionnaires. Blood collection was completed at the

baseline assessment (Johnson et al., 2018) (See Table 1). Participants' first follow-up was four years after the baseline visit and additional follow-up visits were completed approximately every two years. Once enrolled, participants will remain in the study until age 85, unless they withdraw, convert to dementia, or develop another illness that would prevent them from participating or obtaining valid cognitive assessment (Johnson et al., 2018). The following sections will discuss the measures used in examining the specific aims and should not be considered an exhaustive list. For a full list of measures and procedures, see Table 1.

6.2.1 Demographics and Questionnaires

Although it is important to look at all demographic factors, including personal, family, and medical history, etc. as it pertains to the relationship between cognition and nutrition, it is beyond the scope of the current dissertation. The role of a particular diet, MIND diet, as it pertains to cognition is the primary goal of the current dissertation and therefore, the following measures were excluded from data analysis: the Center for Epidemiologic Studies Depression Scale (CES-D), Community Healthy Activities Model Program for Seniors Activities Questionnaire (CHAMPS), Rand Medical Outcomes Study (MOS) Sleep Scale, Epworth Sleepiness Scale (ESS), and the Cognitive Activities Scale and Florida Cognitive Activities Scale. See Table 1 for a list of demographic questionnaires.

Table 1*List of Procedures and Tests in the WRAP Protocol (Johnson et al., 2018)*

Cognitive	Wechsler Abbreviated Scale of Intelligence Wide Range Achievement Test – 3 rd Edition Reading subtest Rey Auditory Verbal Learning Test Boston Naming Test – 2 nd Edition Clock Drawing Test Controlled Oral Word Association Test Wechsler Adult Scale of Intelligence -III: Digit Span & Letter Number Sequencing Trail Making Test Stroop Neuropsychological Screening Test Brief Visuospatial Memory Test – Revised Wechsler Adult Intelligence Scale – Revised: Digit Symbol Wechsler Memory Scale – Revised: Logical Memory Mini-Mental State Examination Animal Fluency Speech samples: open-ended interview questions and picture description COGSTATE: Groton Maze, One Card Learning, Paired Associated, One/Two-Back
Anthropometric and Vitals	Body Mass Index (BMI) Resting Heart Rate Waist-hip Blood Pressure Temperature
Laboratories	Cholesterol, Homocysteine Vitamin B12, Glucose, Insulin, Interleukin-6, hs-CRP Vitamin D: 25(OH)D ₂ , 25(OH)D ₂ total Lipid panel
Biomarkers	Offer enrollment in brain donor program Cerebrospinal fluid substudy Magnetic Resonance Imaging (MRI) substudy Amyloid positron emission tomography (PET) imaging substudy Tau PET imaging substudy
Genetics	Expanded Multi-Ethnic Genotyping Array (MEGA ^{EX}) genomic-wide array Polygenic AD risk score
Participant Questionnaires	Personal, family, and medical history Current medications Women’s health history CES-D Mediterranean-DASH diet Community Healthy Activities Model (CHAMPS) Stress life events Social and caregiving activities Rand MOS Sleep Scale Epworth Sleep Scale Insomnia Severity Index C-pap/devices Cognitive Activities Scale Florida Cognitive Activities Scale
Informant Questionnaires	Quick Dementia Rating Scale Clinical Dementia Rating Informant Questionnaire on Cognitive Decline in the Elderly – Short Form Lawton Instrumental Activities of Daily Living Scale – Modified Version

6.2.1.1 Mediterranean-DASH Diet Intervention for Neurological Delay

A MIND diet score, previously developed by Morris and colleagues (2015), was used to characterize diet component consumption and MIND diet adherence (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015). Morris et al. (2015) developed a MIND diet score using three steps: (1) determined dietary components of the Mediterranean and DASH diets, which included food/nutrients associated with lower incidents of dementia and cognitive decline in the literature (Barnes et al., 2014; Morris & Tangney, 2014; Morris et al., 2003); (2) after administering the modified Harvard semi-quantitative food frequency questionnaire (FFQ) (Morris et al., 2003), relevant food/nutrient items were selected; (3) determined daily servings and assigned a score. The FFQ was validated on a sample of older Chicago community residents. It contains 144 food items and asks participants to report the frequency of consumption over the past 12 months.

The MIND diet has 10 healthy food groups associated with better brain health including green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine. Additionally, there are five components considered unhealthy food groups including red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food. Participants reported frequency of consumption and assigned a 0, 0.5, or 1 to characterize food item portion (Table 2). The only exception was olive oil, which was rated dichotomously (*0 = Not the primary oil used for cooking in the home* and *1 = Primary oil used for cooking in the home*). A total MIND diet score was calculated by summing all 15 component scores (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015), with a possible total score of 15 and higher scores indicating greater diet adherence. Range in the WRAP, according to a recent study by Mueller et al., 2020, was 3-14 ($M = 9.4$, $SD = 1.9$).

Table 2*MIND Diet Component Scoring*

	0	0.5	1
Green Leafy Vegetables ^a	≤ 2 servings/wk	> 2 to < 6/wk	≥ 6 servings/wk
Other Vegetables ^b	< 5 servings/wk	5 – < 7/wk	≥ 1 servings/day
Berries ^c	< 1 serving/wk	1/wk	≥ 2 servings/wk
Nuts	< 1/month	1/month - < 5/wk	≥ 5 servings/wk
Olive Oil	Not primary oil		Primary oil used
Butter, Margarine	> 2 T/d	1-2/day	<1 T/day
Cheese	7+ servings/wk	1-6/wk	<1 serving/wk
Whole Grains	< 1 serving/day	1-2/day	≥ 3 servings/day
Fish (not fried) ^d	Rarely	1-3/month	≥ 1 meals/wk
Beans ^e	< 1 meal/wk	1-3/wk	> 3 meals/wk
Poultry (not fried) ^f	< 1 meal/wk	1/wk	≥ 2 meals/wk
Red Meat and Products ^g	7+ meals/wk	4-6/wk	< 4 meals/wk
Fast Fried Foods ^h	4+ times/wk	1-3/wk	< 1 times/wk
Pastries and Sweets ⁱ	7+ servings/wk	5-6/wk	< 5 servings/wk
Wine	> 1 glass/day or never	1/month-6/wk	1 glass/d

Note. MIND diet total score is calculated by summing all 15 components.

^akale, collards, greens; spinach; lettuce/tossed salad

^bgreen/red peppers, squash, cooked carrots, raw carrots, broccoli, celery, potatoes, peas or lima beans, potatoes, tomatoes, tomato sauce, string beans, beets, corn, zucchini/summer squash/eggplant, coleslaw, potato salad

^cstrawberries

^dbeans, lentils, soybeans

^etuna sandwich, fresh fish as a main dish; not fried fish cakes, sticks, or sandwiches

^fchicken or turkey sandwich, chicken or turkey as main dish and never eat fried at home or away from home

^gcheesburger, hamburger, beef tacos/burritos, hot dogs/sausages, roast beef or ham sandwich, salami, bologna, or other deli meat sandwich, beef (steak, roast), or lamb as main dish, pork or ham as main dish, meatballs or meatloaf

^hHow often do you eat fried food away from home (like French fries, chicken nuggets)?

ⁱbiscuit/roll, poptarts, cake, snack cakes/twinkies, danish/sweetrolls/pastry, donuts, cookies, brownies, pie, candy bars, other candy, ice cream, pudding, milkshakes/frappes

Since the WRAP began, there were updates in the MIND diet questionnaire, and therefore, coding needed to be adjusted from the original publication (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015). Guidelines described in Mueller et al. (2020) include the following:

“Responses were converted to real numbers where possible. If the conversion didn’t translate to a real number, or if the resulting number was less than zero, the response was treated as a missing value. It should be noted that if the participant responded with “>” a number, a value of “.2” was added to the converted value, i.e., a field value of “> 1” was assigned a value of “1.2”. Likewise, if a “<” was found at the beginning of the field, a value of “.2” was subtracted from the converted value, i.e., a field value of “< 1” was assigned a value of “.8”. (p.15)

Any missing field values were not included in the following:

“MIND Diet Score” calculation. For those participants with missing values, a linear “extrapolated sum” was computed based on the number of existing scores and total number of items. For example, if there were three responses missing, and the sum of all scores present was 6.5, then the extrapolated sum would be calculated as follows: $(6.5 / 12) * 15 = 8.125$. This coding scheme was implemented due to participant reports that did not fall within any of the three specified ranges of the published criteria (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015).” (p. 15)

6.3 Cognitive Measures

The WRAP protocol includes a comprehensive cognitive assessment at the baseline visit. Cognitive assessment measures assessed the following domains: cognitive screening, intellectual functioning, verbal and visual learning/memory, language, visuospatial and construction abilities, processing speed, attention and working memory, and executive functioning. Subsequent visits included additional neuropsychological assessment, but the cognitive assessment protocol was limited for some study participants due to the SARS COV2 pandemic. All neuropsychological measures included in the WRAP protocol are well-validated measures of

cognitive functioning. For a list of all cognitive measures, see Table 1. Cognitive measures relevant to the current dissertation are described below.

6.3.1 Neuropsychological Patterns in Alzheimer's Disease

Typical AD is often marked by initial memory impairment for newly acquired information along with word-finding difficulty, including deficits in memory consolidation and rapid loss of information (Saykin & Rabin, 2014). Also seen early in the disease process is confrontation naming difficulties. As AD progresses, other cognitive functions become affected by the neuropathological changes. These changes include moderate to severe impairments in attention, letter fluency, category fluency, word knowledge, anterograde memory storage (storage of new memories after AD onset) and proactive memory interference, retrograde memory (memories before the onset of AD), praxis, and visuoperceptual functions (Tröster & Packwood, 2014). Additionally, there are mild to moderate impairments in problem-solving/cognitive flexibility/conceptualization, anterograde encoding, and visuoconstructional functions. In most typical AD cases, anterograde retrieval can be mildly impaired or unimpaired. Generally, speech remains intact (Tröster & Packwood, 2014).

6.3.2 Learning and Memory

Learning is defined as the process of acquiring new information into memory, whereas memory is defined as the acquisition and retention of information (*INS Dictionary of Neuropsychology and Clinical Neuroscience*, 2015). There are many different types of memory, and sometimes learning and memory can be characterized functionally, such as verbal and visual memory (*INS Dictionary of Neuropsychology and Clinical Neuroscience*, 2015). The WRAP study included two measures of verbal learning, the Rey Auditory Verbal Learning Test

(RAVLT) and the Logical Memory subtest of the Wechsler Memory Scale – Revised (WMS-R). The WRAP protocol also included one visual memory measure, the Brief Visuospatial Memory Test – Revised (BVMT-R), that will not be included in analyses and therefore, will not be described in detail.

6.3.2.1 Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) is a measure of verbal memory (Schmidt, 1996). Individuals are presented with a list of 15 words across five learning trials. Following each trial, the participant is asked to immediately recall the presented words. The examiner next presents a distractor list before asking for immediate recall of the original list once more, followed by 20-30 minute delayed word recall.

6.3.2.2 Wechsler Memory Scale – Revised

The Wechsler Memory Scale – Revised (WMS-R) is an adult memory scale (Wechsler, 1987). It contains eight short-term memory tests, four delayed-recall subtests, and a brief screening of mental status. The WRAP study included one short-term memory test and the associated delayed recall subtest, Logical Memory I and II. Designed to measure episodic memory, participants are read two short stories and asked to immediately recall details of the story. Following a delay (20 minutes), participants are asked to recall details of the story again and complete forced-choice recognition.

6.3.3 Processing Speed

Processing speed, or speed of mental processing, was assessed with three measures, according to the WRAP protocol. These measures included Digit Symbol Substitution Test, Trail Making Test – Part A (TMT-A), and Stroop Color Task.

6.3.3.1 Wechsler Adult Intelligence Scale – Revised

The Wechsler Adult Intelligence Scale – Revised (WAIS-R) is an earlier version of the current WAIS (Wechsler, 1981). The goal of the WAIS-R, however, remains consistent with current WAIS measures: to measure cognitive and intellectual functioning. It includes a Full-Scale IQ measure, two index scores, Verbal IQ and Performance IQ, and 11 subtests. From the WAIS-R, the WRAP study selected one subtest, Digit Symbol Substitution Test, to include in the protocol. The Digit Symbol Substitution Test measures visual motor speed, attention, and visuoperceptual functions. Participants are required to transcribe a unique geometric symbol with the corresponding number based on a key that contains numbers from 1 to 9.

6.3.3.2 Trail Making Test Part A

The Trail Making Test (TMT) is commonly used as an indicator of visual scanning, graphomotor speed, and executive function. It was included in the Halstead-Reitan Neuropsychological Battery in 1958 (Reitan, 1958). There are two conditions, TMT Part A (TMT-A) and TMT Part B (TMT-B). In TMT-A, subjects are asked to connect randomly arranged circles containing numbers 1-25 in number order, as quickly as possible. It is considered a measure of processing speed. TMT-B measures executive functioning, including set-shifting, and therefore, is discussed in the following section (*Executive Functioning*).

6.3.3.3 Stroop Neuropsychological Screening Test

The Stroop Neuropsychological Screening Test (Stroop) is a brief assessment for cognitive processing and the ability to inhibit cognitive interference (Stroop, 1935; Trenerry et al., 1989). There are three conditions: the Word Task, the Color Task, and the Color-Word Task. For the Word Task, participants read a list of colored words in black ink. For the Color Task,

participants are asked to read aloud a list of color names where the name is printed in its matching color. The Color-Word Task is a measure of executive functioning and therefore, will be discussed in the following section (*Executive Functioning*).

6.3.4 Executive Functioning

Executive functions are complex and are generally defined as the intrinsic ability to respond adaptively to novel situations, based on cognitive, emotional, and social skills (Lezak et al., 2012). There are multiple proposed models in attempt to conceptualize the various cognitive abilities that make up this domain. One popular model conceptualizes executive function as four main components: (1) volition; (2) planning and decision making; (3) purposeful action; and (4) effective performance (Lezak et al., 2012). The WRAP protocol included two measures that are generally considered to capture aspects of executive functioning. These include Trail Making Test Part B (TMT-B) and Stroop-Color Word Task.

6.3.4.1 Trail Making Test Part B

The Trail Making Test (TMT) is commonly used as an indicator of visual scanning, graphomotor speed, and executive function. It was included in the Halstead-Reitan Neuropsychological Battery in 1958 (Reitan, 1958). There are two conditions, TMT Part A (TMT-A) and TMT Part B (TMT-B). Unlike TMT-A, which focuses primarily on visual scanning, TMT-B is considered a measure of executive function. In TMT-B, subjects are asked to alternate between numbers and letters in sequential order, as quickly as possible. This requires the ability to flexibly shift between two cognitive sets, letters and numbers. If both parts are completed, a difference score (TMT-B – TMT-A) can be calculated.

6.3.4.2 Stroop Neuropsychological Screening Test

As mentioned previously, the Stroop is a brief assessment for cognitive processing and the ability to inhibit cognitive interference (Stroop, 1935; Trener et al., 1989). In the Color-Word Task, the third condition, participants are asked to name the ink of the colored word, rather than reading the word, which requires one to inhibit a natural response (word reading) for a different response (color naming).

6.3.5 Theoretical Composite Scores and Empirical Factor Scores

Rather than running an additional factor analysis, the current dissertation focused on existing theoretically derived cognitive composites and empirically derived factor scores to eliminate redundancy. Previous data analyses (Dowling et al., 2010; Jonaitis et al., 2019; Koscik et al., 2014) have examined five cognitive factors using factor analysis (Table 3). Notably, factor analysis was guided by theory, but specific factor loadings were driven by WRAP data (Jonaitis et al., 2019). Please see Table 3 for neuropsychological measures included in the cognitive factors scores. The five, previously established, factor scores included immediate learning (Empirical Immediate Learning), story recall (Empirical Story Recall), delayed recall (Empirical Delayed Memory), executive function (Empirical Speeded Flexibility), and visuospatial learning (Empirical Brief Visuospatial Memory Test (BVRT)). Of note, empirical factor analysis suggested alternate division of immediate and delayed memory. Empirical Immediate Learning includes AVLT immediate trials 1 and 2, whereas Empirical Delayed Recall included information from trials 3-5 and delayed recall (Jonaitis et al., 2019). The current dissertation will examine three of the empirical factors as cognitive outcomes: Empirical Immediate Memory, Empirical Story Recall, and Empirical Speeded Flexibility.

Table 3*Empirically Derived Cognitive Factor Scores*

Raw Scores	Empirical Immediate Learning	Empirical Story Recall	Empirical Delayed Recall	Empirical BVMT	Empirical Speeded Flexibility
Rey AVLT Total	X		X		
Rey AVLT Delayed			X		
WMS-R Logical Memory - I		X			
WMS-R Logical Memory – II		X			
BVMT-R Total				X	
BVMT-R Delayed				X	
Stroop Color-Word					X
TMT Part A					X
TMT Part B					X

Note. Rey AVLT = Rey Auditory Verbal Learning Test Total; WMS-R = Wechsler Memory Scale – Revised; BVMT-R = Brief Visual Memory Test – Revised; TMT = Trail Making Test; WAIS-R = Wechsler Adult Intelligence Scale – Revised.

Theoretically derived composite scores (Table 4) using the WRAP data have also been examined (Clark et al., 2018). The neuropsychological measures included in the theoretical cognitive composites are listed in Table 4. Cognitive composite scores include immediate learning (Theoretical Immediate Memory), delayed recall (Theoretical Delayed Memory), and executive functioning (Theoretical Executive Functioning) (Clark et al., 2018). The current dissertation will also examine the three of the theoretical composites as cognitive outcomes.

Table 4*Theoretically Derived Cognitive Composite Scores*

Raw Scores	Theoretical Immediate Memory	Theoretical Delayed Recall	Theoretical Executive Functioning
Rey AVLT Total	X		
Rey AVLT Delayed		X	
WMS-R Logical Memory - I	X		
WMS-R Logical Memory – II		X	
BVMT-R Total	X		
BVMT-R Delayed		X	
Stroop Color-Word			X
TMT Part B			X
WAIS-R Digit Symbol			X

Note. Rey AVLT = Rey Auditory Verbal Learning Test Total; WMS-R = Wechsler Memory Scale – Revised; BVMT-R = Brief Visual Memory Test – Revised; TMT = Trail Making Test; WAIS-R = Wechsler Adult Intelligence Scale – Revised.

6.4 Anthropometric, Vitals, and Laboratories

At each study visit, anthropometric measures (measurements and proportions of the human body) and vitals were obtained. Measurements included BMI, resting heart rate, waist and hip measurement, blood pressure, and temperature. Blood samples were also collected for laboratory and genetic assessment. For a full list of laboratories, see Table 1.

6.5 Biomarkers and Genetic Blood Draw Procedure

Biomarkers were collected using CSF, magnetic resonance imaging (MRI), along with amyloid and tau PET imaging. For detailed explanation of the MRI protocol, see Johnson and colleagues, 2018. For a list of biomarker procedures, see Table 5.

Genetic variables are listed in Table 5. APOE e2/e3/e4, along with 20 common genetic variants from the International Genomics of Alzheimer's Project consortium (Lambert et al., 2013), low frequency variants in TREM2 (triggering receptor expressed on myeloid cells 2) (Guerreiro et al., 2013; Jonsson & Stefansson, 2013), and phospholipase D3 (PLD3) (Cruchaga et al., 2014) were genotyped. Duplicate quality control samples had 99.9% concordance. Additionally, various polygenic risk scores are derived, including an APOE risk score, characterizing the contribution and risk of each single nucleotide polymorphism (Johnson et al., 2018). Although there were 24 at-risk AD genes collected as part of the WRAP study, the current proposal only analyzed APOE risk because possessing just one copy of the APOE-e4 allele is associated with a three-fold risk for developing AD, while inheriting two copies of the e4 allele increases risk by eight-to-12 fold (Holtzman et al., 2012; Loy et al., 2014; Michaelson, 2014). Importantly, there is some research that suggests APOE genotype may interact with modifiable and nonmodifiable risk factors for AD differently.

The WRAP APOE risk score was calculated according to the odds ratio of e2/e3/e4 genotype as indicated in the meta-analysis of APOE genotype frequencies reported in AlzGene (Weuve, McQueen, et al., 2018). These ratios were based on studies of white individuals and were calculated using the e2/e2/genotype as reference (e2/e2 OR = 1) including the following: e2/e3 OR = 1.38, e3/e3 OR = 2.00, e2/e4 OR = 4.45, e3/e4 OR = 6.78, e4/e4 OR = 25.84 (Darst et al., 2017). APOE risk scores reflected in the current study are the natural logarithm of the OR.

Table 5*Biomarker, Genetic, and Lab Procedure List*

Imaging

CSF
 Amyloid PET
 Tau PET
 T1-weighted volume
 T2 MRI
 T2 FLAIR
 DTI
 rs-fMRI

Genetic and Lab Procedures

APOE
 Polygenic risk score
 Plasma (Heparin)
 Plasma (EDTA)
 Plasma (Any)
 Glucose Levels
 Cholesterol
 C-reactive protein
 Homocysteine

Note. CSF = cerebrospinal fluid; PET = positron emission tomography; MRI = magnetic resonance imaging; FLAIR = fluid attenuated inversion recovery; DTI = diffusion tensor imaging; rs-fMRI = resting state functional MRI; APOE = apolipoprotein.

CHAPTER 7

ANALYTIC OVERVIEW

Descriptive statistics and baseline group comparisons were investigated using IBM SPSS Statistics v28. Given cognitive outcomes were z-score composites, a z-score cutoff of +/- 3.00 (three standard deviations above the mean) was used to determine univariate outliers which is a more conservative approach to capture potential outliers that may also be influential (Tabachnick & Fidell, 2018). Even with a more conservative approach, only 17 outliers were removed from the Theoretical Immediate Memory (TIM) composite, 16 outliers were removed from the Theoretical Delayed Memory (TDM) composite, and 35 outliers were removed from the Theoretical Executive Functioning (TEF) composite. Regarding empirically derived factor scores, 32 outliers were removed from the Empirical Immediate Memory (EIM) factor, three outliers were removed from the Empirical Story Recall (ESR) factor, and 34 outliers were removed from the Empirical Speeded Flexibility (ESF) factor. Assumptions of normality for each outcome variable were assessed and all were nonnormally distributed ($ps < .05$) using the Kolmogorov-Smirnov test, and the data presented with positive skewness and kurtosis. A logarithmic transformation was applied, but it did not correct for skewness. Therefore, nonparametric correlations were conducted and reported for predictor and outcome variables (Table A1).

Latent growth curve (LGC), or latent growth modeling (LGM), allows for examination of longitudinal change (Keith, 2019). First, the growth portion of the model were estimated. Next the influences on growth or the variables affected by growth were added. To examine Aims one through three, nonmodifiable risk factors (age, gender, and APOE-e4 risk) and modifiable risk

factors (MIND diet and WHR) were added as predictors to the model. The initial structural model determines whether there is significant heterogeneity in growth trajectories (i.e., intercept and slope) of cognitive abilities at various time points that are explained by the risk factors (i.e., predictors). Established guidelines suggest the sample size should be greater than 10 times the number of estimated parameters (Raykov & Marcoulides, 2000). In the most complex initial structural model, there are 26 estimated parameters. Using the guidelines previously mentioned, each model needs at minimum 260 participants to conduct proposed longitudinal analysis.

Latent Growth Curve (LGC) was conducted using IBM SPSS Amos v29 to test the longitudinal relationship between nonmodifiable (age, gender, and genetic risk) and modifiable risk factors (MIND diet adherence and physical health) as it pertains to cognition. The interaction, or moderating effect, of APOE status was also assessed using LGC. Because the MIND diet measure was not added to the WRAP study until V4, LGC analysis will estimate change across time from V4 to V6. It is well-established that the presence of missing data in structural equation modeling (SEM) can be problematic and there is not one correct method for managing it. Missing data were addressed using full information maximum likelihood estimation, rather than more traditional approaches such as listwise deletion, pairwise deletion, or single imputation. Although using more traditional approaches to missing data will ensure a complete dataset for SEM analyses, traditional approaches come with their own set of limitations. For example, listwise deletion assumes data are missing at complete random (Arbuckle, 1996; Brown, 1994) and tends to be associated with reduced sample size, reducing statistical power and increases risk for nonconvergent solutions and incorrect standard errors (Anderson & Gerbing, 1984; Boomsma, 1982; Marsh & Balla, 1994; Marsh et al., 1988). Maximum likelihood (ML) estimation is the most widely used criterion among SEM because it is

theoretically based, and it prevents the loss of data in longitudinal studies (Byrne, 2010). It utilizes all information of the observed data, including means and variances for missing portions of a variable, given the observed aspects of other variables (Wothke, 1998). Furthermore, studies comparing methods of full information maximum likelihood and listwise deletion revealed there is little difference in the estimation bias (Carter, 2006). When utilizing ML estimation, the approach to fitting SEM models (including LGC models) differs in two ways (Arbuckle & Wothke, 1999). First, in addition to fitting the hypothesized model, a saturated model computing a χ^2 value and fit indices must be computed. Second, execution time can be more extensive.

Although ML estimation allows for more longitudinal data to be included in the model, there are some limitations to consider. First, some aspects of the model, including modification indices cannot be estimated. Second, common methods of assessing multivariate normality, using Mardia's multivariate kurtosis statistic (Gao & Mokhtarian, 2008), and identifying multivariate outliers, using Mahalanobis distances (D^2) (Gao & Mokhtarian, 2008) cannot be utilized. As an alternative, the linear relationships can be assessed prior to LGC modeling using regression assumptions including heteroscedasticity and multicollinearity (Field, 2009). Therefore, QQ plots of outcome residuals were inspected for heteroscedasticity; variance inflation factor (VIF) and tolerance (TOL) were assessed to detect multicollinearity; and the Cook's distance (Cook's d) estimate was used to determine influential data points across each time point. Upon examination, QQ plots were negative for heteroscedasticity and multicollinearity.

Influential data points using Cook's d were assessed by each outcome variable. First, Cook's d values were plotted for each of the three time points for each outcome variable (TIM, TDM, and TEF). Upon visual inspection of Cook's d plots, outliers that significantly deviated

from the remaining datapoints and/or regression line were removed. In addition, Cook's d values were individually assessed for all cases and removed if the value was >1 (Cook & Weisberg, 1982). Although D^2 can also be assessed using regression, the cutoff point is not easily established (Field, 2009). Examination of the TIM composite revealed one influential outlier which was removed from V4 and V5, and no datapoints were removed at V6. Regarding the TDM composite, one influential outlier was removed from V4 and V5, and no datapoints were removed at V6. Examination of the TEF composite revealed one outlier removed at V4 and V6, but no datapoints were removed at V5. No influential outliers were observed on empirical composite scores.

CHAPTER 8

RESULTS

8.1 Demographics

For participant demographics, see Table 6. Overall, majority of the sample was middle age at baseline ($M_{age} = 54.52$ years, $SD = 6.81$) and V4 ($M_{age} = 63.78$, $SD = 6.40$), female (70.6%), white/Caucasian (97.6%), and cognitively unimpaired (85.9%). There were 1572 participants who underwent genetic testing. The first allele in the genotype was either e2 (11.9%), e3 (83.5%), or e4 (4.6%). Similarly, the second allele in the genotype was either e2 (.40%), e3 (59.9%), or e4 (39.6%).

Table 6*Baseline Demographic Characteristics*

	<i>N (%)</i>	<i>Mean (SD)</i>
Age	1642	54.52 (6.81)
Gender		
Male	478 (29.30)	
Female	1153 (70.80)	
Other	2 (.20)	
Race		
American Indian/Native American	10 (.70)	
Asian	2 (.10)	
Black/African American	117 (7.60)	
White/Caucasian	1370 (89.20)	
Spanish/Hispanic	37 (2.40)	
Education	1531	16.01 (2.80)
APOE Risk Score	1572	1.19 (.75)
.00	7 (.40)	
.32	127 (7.10)	
.70	815 (51.80)	
1.49	53 (3.40)	
1.91	498 (31.70)	
3.25	72 (4.60)	

Note. APOE = apolipoprotein. The APOE risk scores reflected in the table are natural logarithms of the OR (see *Materials and Methods* section for additional information).

Examination of dietary components at V4 (Table 7) revealed that majority of the participants consumed ≥ 6 servings of green leafy vegetables per week (67.4%), ≥ 1 servings per day of other vegetables (88.4%), ≥ 2 servings per week of berries (59.7%), ≥ 5 servings per week of nuts (58.5%), butter/margarine 1-2 times per day (54.1%), cheese 1-6 times per week (77%), whole grains 1-2 times per day (68.5%), ≥ 1 fish meals per week (69.1%), beans 1-3 times per week (72.1%), ≥ 2 poultry meals per week (60%), and < 4 red meat meals per week (60.8%). Furthermore, majority of participants reported eating fast food < 1 time per week (61.1%), < 5 servings of pastries/sweets (58.5%), and consuming > 1 glass per day or never (63.3%). Nearly 73% of participants indicated olive oil is not their primary cooking oil.

Table 7

V4 MIND Diet Component Frequencies

	<i>N (%)</i> 0	<i>N (%)</i> 0.5	<i>N (%)</i> 1
Green Leafy Vegetables	92 (19.60)	61 (13)	317 (67.40)
Other Vegetables	54 (11.40)	1 (.20)	418 (88.40)
Berries	90 (19.10)	100 (21.20)	281 (59.70)
Nuts	125 (26.50)	71 (15)	276 (58.50)
Olive Oil	347 (73.50)	-	125 (26.50)
Butter, Margarine	60 (12.70)	255 (54.10)	156 (33.10)
Cheese	34 (7.30)	359 (77)	73 (15.70)
Whole Grains	68 (14.40)	324 (68.50)	81 (17.10)
Fish (not fried)	109 (23.10)	37 (7.80)	326 (69.10)
Beans	98 (20.90)	339 (72.10)	33 (7)
Poultry (not fried)	42 (8.90)	147 (31.10)	283 (60)
Red Meat and Products	56 (3.40)	129 (27.30)	287 (60.80)
Fast Fried Foods	16 (3.40)	167 (35.50)	288 (61.10)
Pastries and Sweets	125 (26.50)	71 (15)	276 (58.50)
Wine	298 (63.30)	84 (17.80)	89 (18.90)

Note. For reference values associated with 0, 0.5, and 1, please refer to Table 2. MIND diet total score is calculated by summing all 15 components.

8.2 Nonparametric Correlations

Initial nonparametric correlations revealed expected relationships, including positive correlations between WHR, as well as MIND diet adherence, and cognitive outcomes (theoretical composite scores and empirical factor scores) (Table A1, Appendix A). The only exception was that MIND diet total scores were not significantly associated with the ESF factor broadly. Interestingly, there was no significant relationship between APOE risk score and cognitive outcomes. This finding remained consistent when nonparametric correlations among other variables were examined: APOE risk was not significantly associated with cognitive, physical, or diet variables. Regarding diet adherence, MIND diet total scores were not significantly associated with cognition at V4; however, those with higher MIND diet adherence demonstrated significantly higher scores on the EIM factor at V5 and on the ESR factor at V6.

8.3 Outcome Correlations Across Time

Predictor and Outcome descriptive statistics for Visit 4 (Table A2), Visit 5 (Table A4), and Visit 6 (Table A6) are listed in Appendix A. Tables A3, A5, and A7 (Appendix A) provide nonparametric correlations of predictors and outcome variables at each time point. Furthermore, Table A8 (Appendix A) included nonparametric correlations of cognitive outcomes, comparing domains across visits. As expected, theoretical composite and empirical factor scores were significantly correlated across the three time points ($ps \leq .001$).

8.4 Latent Growth Curve Modeling

As mentioned in the *Methods & Materials* section, rather than running additional factor analysis, the current dissertation used existing theoretically derived composite scores (Table 4) and empirically derived factor scores (Table 3) as outcome variables for the LGC model. To

determine model fit, several measures of fit including nonsignificant chi-square, root mean square error of approximations (RMSEA) $\leq .05$, comparative fit index (CFI) $\geq .95$, Tucker-Lewis index (TLI) $\geq .95$, and the Akaike information criterion (AIC; used for comparing competing models) (Keith, 2019). Notably, the chi-square statistic and RMSEA value can be especially sensitive and sometimes, are not the best indicators of overall fit. Therefore, all measures of fit were examined upon data analysis.

Theoretical composite and empirical factor scores at Visits 4, 5, and 6 were used for modeling the growth curves, in two separate models. Model analyses first examined the within-domain covariance estimates between the intercepts and slopes. Selected predictors were theoretically driven and included nonmodifiable risk factors for AD (i.e., age, gender, APOE risk score) and modifiable risk factors (i.e., MIND diet Score and waist-to-hip ratio).

8.4.1 Initial Hypothesized Models

8.4.1.1 Theoretical Immediate Memory Composite Scores

The initial hypothesized model, a single-domain (TIM Composite Scores V4-6) LCG is represented in Figure B1 (Appendix B). Composite scores for each visit were then used to form the overall TIM intercept and slope variables. Parameters from the intercept and slope to the observed variables (TIM Composites Visits 4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6, respectively, which occurred approximately two years apart; therefore, reflecting equal time between visits. Composite score covariances were allowed to covary over time. Residuals for each time point were freely estimated at each visit.

Regarding initial findings of the TIM hypothesized model, goodness-of-fit statistics revealed a well-fitting model, $\chi^2(3) = 15.18, p = .002$ (TLI = .99; CFI = .99; RMSEA = .05). In Table 8, the estimated values for all parameters of primary interest are reported which correspond with Figure B1 (Appendix B). The TIM intercept indicates the average Immediate Memory Composite Score at initial status (V4) and the TIM slope represents the average range of change over V4, 5, and 6. The TIM intercept is not statically significant, which indicates that the average Immediate Memory Composite Score did not initially differ from zero at V4 (estimate = -.025) and this score increased on average by .02 at V5 and 6. As noted in Table 8, the TIM slope was statistically significant, suggesting that as time progressed from V4 to V6, Immediate Memory Composite Scores significantly improved. The covariance between the residuals associated with the TIM intercept and rate of change in Immediate Memory Composite Scores (slope) across participants was not statistically significant, suggesting that the initial Immediate Memory Composite Scores (low vs. high) did not significantly influence the direction of change across time. Lastly, Table 8 provides estimates of the error variance associated with observed variables at each visit (E1, E2, E3). The error terms associated with V4, 5, and 6 were statistically significant. This finding suggests strong interindividual differences in both initial Immediate Memory Composite Scores at Visit 4 and their change over time warranting further investigation into possible predictors account for the error variance.

Table 8*Parameter Estimates for TIM Composite Scores Hypothesized Model*

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
TIM Intercept	IMean	-.025	.37
TIM Slope	SMean	.019	< .001**
Intercept/Slope Covariance		-.004	.57
Error Variances			
TIM Visit 4	E1 Var	.234.	< .001**
TIM Visit 5	E2 Var	.234	< .001**
TIM Visit 6	E3 Var	.234	< .001**

Note. $N = 1638$. $\chi^2(3) = 15.18$, $p = .002$ (TLI = .99; CFI = .99; RMSEA = .05). Table corresponds with Figure B1. $p \leq .01$ **; $p \leq .05$ *. TIM = Theoretical Immediate Memory.

8.4.1.2 Theoretical Delayed Memory Composite Scores

The initial hypothesized model including TDM Composite Scores for each visit (TDM Composite V4-6) is represented in Figure B2 (Appendix B). Composite scores for each visit were then used to form the overall TDM intercept and slope variables. Parameters from the intercept and slope to the observed variables (TDM Composites Visits 4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6, respectively, which occurred approximately two years apart; therefore,

reflecting equal time between visits. Composite score covariances were allowed to covary over time. Residual for each time point were freely estimated at each visit.

Regarding initial findings of the TDM hypothesized model, goodness-of-fit statistics revealed an exceptionally well-fitting model, $\chi^2(3) = 2.76, p = .43$ (TLI = 1.00; CFI = 1.00; RMSEA = .00). Although CFI and TLI indices might raise concern that the model was overfitted to the data, this was not the case and rather, these exceptionally high values are indicative of a well-fitting model due to the simplistic structure of the initial hypothesized model (Byrne & Crombie, 2003). Table 9 displays the estimated values for all parameters of primary interest, which correspond to Figure B2 (Appendix B). The TDM intercept indicates the average initial Delayed Memory Composite score (V4), whereas the TDM slope represents the average range of change over V4, 5, and 6. The TDM intercept is not statistically significant, which suggests that the average Delayed Memory Composite Score did not initially differ from zero at V4 (estimate = -.037) and this score increased on average by .033 at V5 and 6. As noted in Table 9, the TDM slope was statistically significant suggesting that as time progresses from V4 through Visit 6, Delayed Memory Composite Scores significantly improved. The covariance between the residuals associated with the TDM intercept and rate of change in Delayed Immediate Memory Composite Scores (slope) across participants was not statistically significant. This finding suggests that the initial Delayed Memory Composite Scores (low vs. high) did not significantly influence the direction of change across time. Lastly, Table 9 provides estimates of the error variance associated with observed variables at each visit (E1, E2, and E3). The error terms associated with V4, 5, and 6 were statistically significant. This finding suggests strong interindividual differences in both initial Delayed Memory Composite Scores at V4 and their

change over time, warranting further investigation into possible predictors accounting for the error variance.

Table 9

Parameter Estimates for TDM Composite Scores Hypothesized Model

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
TDM Intercept	IMean	-.037	.18
TDM Slope	SMean	.033	< .001**
Intercept/Slope Covariance		-.009	.127
Error Variances			
TDM Visit 4	E1 Var	.229	< .001**
TDM Visit 5	E2 Var	.229	< .001**
TDM Visit 6	E3 Var	.229	< .001**

Note. $N = 1638$. $\chi^2(3) = 2.76, p = .43$ (TLI = 1.00; CFI = .1.00; RMSEA = .00). Table corresponds with Figure B2. $p \leq .01$ **; $p \leq .05$ *. TDM = Theoretical Delayed Memory.

8.4.1.3 Theoretical Executive Functioning Composite Scores

The initial hypothesized model including TEF Composite Scores for each visit (TEF Composite V4-6) is represented in Figure B3 (Appendix B). Composite scores for each visit were then used to form the overall TEF intercept and slope variables. Parameters from the intercept and slope to the observed variables (TEF Composites V4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6,

respectively, which occurred approximately two years apart; therefore, reflecting equal time between visits. Composite score covariances were allowed to covary over time. Residual for each time point were freely estimated at each visit.

Regarding initial findings of the TEF hypothesized model, goodness-of-fit statistics revealed an exceptionally well-fitting model, $\chi^2(3) = .51, p = .92$ (TLI = 1.00; CFI = 1.00; RMSEA = .00). Like the previous model, the CFI and TLI indices are indicative of a well-fitting model due to the simplistic structure of the initial hypothesized model, although exceptionally high (Byrne & Crombie, 2003). Table 10 displays the estimated values for all parameters of primary interest, which correspond with Figure B3 (Appendix B). The TEF intercept indicates the average initial Executive Functioning Composite Score (V4), whereas the TEF slope represents the average rate of change over V4, 5, and 6. The TEF intercept is not statistically significant, indicating that the average Executive Functioning Composite Score did not initially differ from zero at V4 (estimate = -.005). As noted in Table 10, the TEF slope was statistically significant suggesting that as time progresses from V4 through V6, Executive Functioning Composite Scores significantly decreased by .039 at V5 and 6. The covariance between the residuals associated with the TEF intercept and rate of change in Executive Functioning Composite Scores (slope) across participants was statistically significant (estimate = .007). This finding suggests that participants with a high initial TEF Composite Scores (at V4) tend to have greater rates of increase across visits compared to those with lower TEF Composite Scores. Lastly, Table 10 provides estimates of the error variance associated with observed variables at each visit (E1, E2, and E3). The error terms associated with V4, 5, and 6 were statistically significant. This finding suggests strong interindividual differences in both initial TEF

Composite Scores at V4 and their change over time, warranting further investigation into possible predictors accounting for the error variance.

Table 10

Parameter Estimates for TEF Composite Scores Hypothesized Model

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
TEF Intercept	IMean	-.005	.86
TEF Slope	SMean	-.039	< .001**
Intercept/Slope Covariance		.007	.046*
Error Variances			
TEF Visit 4	E1 Var	.101	< .001**
TEF Visit 5	E2 Var	.101	< .001**
TEF Visit 6	E3 Var	.101	< .001**

Note. $N = 1640$. $\chi^2(3) = .51, p = .92$ (TLI = 1.00; CFI = .1.00; RMSEA = .00). Table corresponds with Figure B3. $p \leq .01$ **; $p \leq .05$ *. TEF = Theoretical Executive Functioning

8.4.1.4 Empirical Immediate Memory Factor Scores

The initial hypothesized model including EIM Factor Scores for each visit (EIM Factor Scores V4-6) is represented in Figure B4 (Appendix B). Factor scores for each visit were then used to form the overall EIM intercept and slope variables. Parameters from the intercept and slope to the observed variables (EIM Factor Scores V4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6,

respectively, which occurred approximately two years apart; therefore, reflecting equal time between visits. Factor score covariances were allowed to covary over time. Residual for each time point were freely estimated at each visit.

Regarding initial findings of the EIM hypothesized model, goodness-of-fit statistics revealed a well-fitting model, $\chi^2(3) = 10.30, p = .02$ (TLI = .98; CFI = .99; RMSEA = .04). Table 11 displays the estimated values for all parameters of primary interest, which correspond with Figure B4 (Appendix B). The EIM intercept indicates the average Immediate Memory Factor Score at initial status (V4), whereas the EIM slope represents the average rate of change over V4, 5, and 6. The EIM intercept was not statistically significant, indicating that the average Immediate Memory Factor Score did not initially differ from zero at Visit 4 (estimate = -.029). Furthermore, the EIM slope also was not statistically significant, suggesting that as time progressed from V4 through V6, EIM Factor Scores did not significantly differ from zero (estimate = -.003). As such, the covariance between the residuals associated with the EIM intercept and rate of change in Immediate Memory Factor Scores (slope) across participants was not significantly different (estimate = .016). Lastly, Table 11 provides estimates of the error variance associated with observed variables at each visit (E1, E2, and E3). The error terms associated with V4, 5, and 6 were statistically significant, suggesting strong interindividual differences in Immediate Memory Factor Scores over time. However, although the model may appear to warrant further investigation based on error variance assessment, the model will be limited in its ability to capture the variance across time.

Table 11*Parameter Estimates for EIM Factor Score Hypothesized Model*

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
EIM Intercept	IMean	-.029	.232
EIM Slope	SMean	-.003	.645
Intercept/Slope Covariance		.016	.064
Error Variances			
EIM Visit 4	E1 Var	.510	< .001**
EIM Visit 5	E2 Var	.510	< .001**
EIM Visit 6	E3 Var	.510	< .001**

Note. $N = 1640$. $\chi^2(3) = 10.30$, $p = .02$ (TLI = .98; CFI = .99; RMSEA = .04). Table corresponds with Figure B4. $p \leq .01$ **; $p \leq .05$ * . EIM = Empirical Immediate Memory.

8.4.1.5 Empirical Story Recall Factor Scores

The initial hypothesized model including ESR Factor Scores for each visit (ESR Factor Scores V4-6) is represented in Figure B5 (Appendix B). Factor scores for each visit were then used to form the overall ESR intercept and slope variables. Parameters from the intercept and slope to the observed variables (ESR Factor Scores V4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6, respectively, which occurred approximately two years apart; therefore, reflecting equal time

between visits. Factor score covariances were allowed to covary over time. Residual for each time point were freely estimated at each visit.

Regarding initial findings of the ESR hypothesized model, goodness-of-fit statistics revealed an adequate-fitting model, $\chi^2(3) = 17.84, p = .00$ (TLI = .96; CFI = .98; RMSEA = .06). Table 12 displays the estimated values of all parameters of primary interest, which correspond with Figure B5 (Appendix B). The ESR intercept indicates the average Story Recall Factor Score at initial status (V4), whereas the ESR slope represents the average rate of change over V4, 5, and 6. The ESR intercept was statistically significant, indicating that the average Story Recall Factor Score significantly differed from zero at V4 (estimate = -.079). Furthermore, the ESR slope was not statistically significant, suggesting that as time progressed from V4 through V6, Story Recall Factor Scores did not significantly differ from zero (estimate = .003). The covariance between the residuals associated with the ESR intercept and rate of change in Story Recall Factor Scores (slope) across participants was statistically significant (estimate = -.161). This finding suggests that participants with a low initial Story Recall Factor Score (at V4) tend to have greater rates of increase across visits compared to those with higher Story Recall Factor Scores. Lastly, Table 12 provides estimates of the error variance associated with observed variables at each visit (E1, E2, and E3). The error terms associated with V4, 5, and 6 were statistically significant. This finding suggests strong interindividual difference in both initial Story Recall Factor Scores at V4 and their change over time. However, given that the slope was not significantly different than zero, the model will not yield helpful information as it pertains to change in Story Recall Factor Scores over time.

Table 12*Parameter Estimates for ESR Factor Score Hypothesized Model*

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
ESR Intercept	IMean	-.079	.043*
ESR Slope	SMean	.003	.807
Intercept/Slope Covariance		-.161	.019*
Error Variances			
ESR Visit 4	E1 Var	.185	< .001**
ESR Visit 5	E2 Var	.185	< .001**
ESR Visit 6	E3 Var	.185	< .001**

Note. $N = 1642$. $\chi^2(3) = 17.84$, $p = .00$ (TLI = .96; CFI = .98; RMSEA = .06). Table corresponds with Figure B5. $p \leq .01$ **; $p \leq .05$ *. ESR = Empirical Story Recall,

8.4.1.6 Empirical Speeded Flexibility Factor Scores

The initial hypothesized model including ESF Factor Scores for each visit (ESF Factor Scores V4-6) is represented in Figure B6 (Appendix B). Factor scores for each visit were then used to form the overall ESF intercept and slope variables. Parameters from the intercept and slope to the observed variables (ESF Factor Scores V4-6) were fixed, with intercept parameters constrained to a value of 1.0, to allow for interpretation of initial mean values. This constraint reflects a constant intercept value across time for each participant (Duncan et al., 1999). The values 0, 2.0, and 4.0 were assigned to the slope parameters to represent V4, 5, and 6, respectively, which occurred approximately two years apart; therefore, reflecting equal time

between visits. Factor score covariances were allowed to covary over time. Residual for each time point were freely estimated at each visit.

Regarding initial findings of the ESF hypothesized model, goodness-of-fit statistics revealed an adequate-fitting model, $\chi^2(3) = 20.98, p = .00$ (TLI = .99; CFI = .99; RMSEA = .06). Table 13 displays the estimated values of all parameters of primary interest, which corresponds with Figure B6 (Appendix B). ESF intercept indicates the average Speeded Flexibility Factor Score at initial status (V4), whereas the ESF slope represents the average rate of change over V4, 5, and 6. The ESF intercept was not statistically significant, indicating that the average Speeded Flexibility Factor Score was not statistically different from zero at V4 (estimate = .00). The ESF slope was statistically significant, suggesting that as time progressed from V4 through V6, Speeded Flexibility Factor Scores significantly differed from zero (estimate = .010). The covariance between the residuals associated with the ESF intercept and rate of change in Speeded Flexibility Factor Scores (slope) across participants was not statistically significant (estimate = -.071). This finding suggests that initial Speeded Flexibility Factor Scores (low vs. high) did not significantly influence the direction of change across time. Lastly, Table 13 provides estimates of the error variance associated with observed variables at each visit (E1, E2, and E3). The error terms associated with V4, 5, and 6 were statistically significant. This finding suggests strong interindividual differences in both initial Speeded Flexibility Factor Scores at V4 and their change over time. However, given that the slope was not significantly different than zero, the model will not yield helpful information as it pertains to change in Speeded Flexibility Factor Scores over time.

Table 13*Parameter Estimates for ESF Factor Score Hypothesized Model*

Variable	Model Parameter	Estimate	<i>p</i> - value
Mean Estimates			
ESF Intercept	IMean	.000	.99
ESF Slope	SMean	.010	.049*
Intercept/Slope Covariance		.005	.369
Error Variances			
ESF Visit 4	E1 Var	.190	< .001**
ESF Visit 5	E2 Var	.190	< .001**
ESF Visit 6	E3 Var	.190	< .001**

Note. $N = 1632$. $\chi^2(3) = 17.84$, $p = .00$ (TLI = .96; CFI = .98; RMSEA = .06). Table corresponds with Figure B6. $p \leq .01$ **; $p \leq .05$ *. ESF = Empirical Speeded Flexibility.

8.4.2 Initial Structural Models

Previous research has compared empirical and theoretical composite/factor scores and results suggest that the theoretically derived composite scores may lead to time trends more visible because they demonstrated lower intraindividual variability (Jonaitis et al., 2019). Given that model fit among LGC models that had empirically derived cognitive factor scores (i.e., EIM, ESR, and ESF) as outcome variables had significantly poorer fit upon examination of initial hypothesized models (Tables 11, 12, and 13), the structural models including theoretically derived composite scores (i.e., TIM, TDM, and TEF) as outcomes were examined. As mentioned previously, selected predictors were theoretically driven and included nonmodifiable risk factors for AD (i.e., age, gender, APOE risk score) and modifiable risk factors (i.e., MIND diet score

and WHR). Paths are drawn from predictors to initial levels (intercept) and growth levels (slope). In the initially hypothesized models, the intercept and slope were allowed to correlate. These variables are now considered endogenous in the conditional (or initial structural models) models and therefore, cannot correlate directly. Instead, their disturbances are correlated (Keith, 2019). Regression paths flow from each predictor variable to the intercept and slope factors associated with theoretical composite domains.

8.4.2.1 Theoretical Immediate Memory Composite Scores

The initial structural model including TIM Composite Scores for each visit (TIM Composite Scores V4-6) is represented in Figure C1 (Appendix C). Goodness-of-fit statistics revealed poor model fit, $\chi^2(18) = 210.96, p = .00$ (TLI = .77; CFI = .88; RMSEA = .08; AIC = 262.96). In effort to improve model fit, the WHR predictor was removed. Model fit significantly improved, $\chi^2(13) = 28.91, p = .007$ (TLI = .98; CFI = .99; RMSEA = .03; Δ AIC = 190.05). The statistically significant chi-square value was not surprising, given the sensitivity of the test. Positive slope values indicated that TIM increased over time (.129).

Pathway analysis (Table 14) revealed that Gender had positive effects on both initial TIM and on TIM growth over time. More specifically, females scored .09 points higher than males at the initial visit, and females also had a higher rate of change over time (.041 every two years). Furthermore, Age at Visit 4 had statistically significant negative effects on both initial level and growth in TIM. Participants who were older at the initial visit show less change from one visit to the next compared to younger participants (-.003). APOE risk score and MIND diet at Visit 4 did not have statistically significant effects on initial level (APOE risk score = -.067; MIND diet Sum Visit 4 = .026) or growth in TIM (APOE risk score = -.013; MIND diet Sum Visit 4 =

.008). In other words, after controlling for all other variables, the effects on APOE risk and MIND diet were not significant and should be considered having zero effect.

Table 14

Theoretical Immediate Memory Initial Structural Model Unstandardized Regression Weights

Outcome	Pathway	Predictor	Estimate	Standard Error	P value
TIM Intercept	<----	Gender	.089	.042	.034*
TIM Intercept	<----	APOE Risk Score	-.067	.040	.095
TIM Intercept	<----	MIND Score Visit 4	.026	.023	.270
TIM Intercept	<----	Age at Visit 4	-.040	.005	<.001**
TIM Slope	<----	Gender	.041	.010	<.001**
TIM Slope	<----	APOE Risk Score	-.013	.010	.172
TIM Slope	<----	MIND Score Visit 4	.008	.009	.342
TIM Slope	<----	Age at Visit 4	-.003	.001	.002**

Note. $N = 1685$. $\chi^2(13) = 28.91$, $p = .007$ (TLI = .98; CFI = .99; RMSEA = .03). Table corresponds with Figure C1. $p \leq .01$ **; $p \leq .05$ *. TIM = Theoretical Immediate Memory.

8.4.2.2 Theoretical Delayed Memory Composite Scores

The initial structural model including TDM Composite Scores for each visit (TDM Composite Scores V4-6) is represented in Figure C2 (Appendix C). Goodness-of-fit statistics revealed poor model fit, $\chi^2(18) = 213.91$, $p = .00$ (TLI = .75; CFI = .87; RMSEA = .08; AIC = 265.91). In effort to improve model fit, the WHR predictor was removed. Model fit significantly improved, $\chi^2(13) = 35.94$, $p = .001$ (TLI = .96; CFI = .98; RMSEA = .03; Δ AIC = 185.97). The statistically significant chi-square value was not necessarily surprising, given the sensitivity to

large samples (Kline, 2011). Positive slope values indicated that TDM increased over time (.169).

Pathway analysis (Table 15) revealed that Age at Visit 4 had statistically significant negative effects on both initial level and growth in TDM. Participants who were older at the initial visit showed less change from one visit to the next compared to younger participants (-.004). Gender had significant positive effects on growth in TDM over time, but not initial level, suggesting that females had a higher rate of change over time (.035 every two years). APOE risk score and MIND diet at Visit 4 did not have statistically negative effects on initial level (APOE risk score = -.066; MIND Diet Sum Visit 4 = .014) or growth in TDM (APOE risk score = -.009; MIND Diet Sum Visit 4 = .004). In other words, after controlling for all other variables, the effects on APOE risk and MIND diet were not significant and should be considered having zero effect.

Table 15*Theoretical Delayed Memory Initial Structural Model Unstandardized Regression Weights*

Outcome	Pathway	Predictor	Estimate	Standard Error	P value
TDM Intercept	<----	Gender	.075	.040	.058
TDM Intercept	<----	APOE Risk Score	-.058	.037	.123
TDM Intercept	<----	MIND Score Visit 4	.014	.022	.521
TDM Intercept	<----	Age at Visit 4	-.035	.004	<.001**
TDM Slope	<----	Gender	.035	.010	<.001**
TDM Slope	<----	APOE Risk Score	-.009	.009	.322
TDM Slope	<----	MIND Score Visit 4	.004	.009	.676
TDM Slope	<----	Age at Visit 4	-.004	.001	<.001**

Note. $N = 1638$. $\chi^2(13) = 35.94$, $p = .001$ (TLI = .96; CFI = .98; RMSEA = .03). Table corresponds with Figure C2. $p \leq .01$ **; $p \leq .05$ *. TDM = Theoretical Delayed Memory.

8.4.2.3 Theoretical Executive Functioning Composite Scores

The initial structural model including TEF Composite Scores for each visit (TEF Composite Scores V4-6) is represented in Figure C3 (Appendix C). Goodness-of-fit statistics revealed poor model fit, $\chi^2(18) = 215.51$, $p = .00$ (TLI = .83; CFI = .92; RMSEA = .08; AIC = 267.91). In effort to improve model fit, the WHR predictor was removed. Model fit significantly improved, $\chi^2(13) = 41.43$, $p = .000$ (TLI = .97; CFI = .99; RMSEA = .04; Δ AIC = 182.48). The statistically significant chi-square value was not necessarily surprising, given the sensitivity of the test. Positive slope values indicated that TEF increased over time (.318).

Pathway analysis (Table 16) revealed that Gender had positive effects on initial TEF revealing that females tended to score higher on the TEF composite (.086 points higher)

compared to males at the initial visit; however, Gender demonstrated no significant effect on TEF growth over time. Age at Visit 4 had statistically significant negative effects on both initial level and growth in TEF. This finding suggests that participants who were older at the initial visit show less change from one visit to the next compared to younger participants (-.003). Unlike the other models, APOE risk score had significant effects on the initial TEF level (-.072), but not on TEF growth over time, suggesting participants with higher APOE risk scores had lower TEF composite scores at Visit 4. Furthermore, MIND Diet Scores did not have significant effects on TEF at the initial visit; however, MIND Diet Scores had significant negative effects on TEF growth over time. This finding suggests those with higher initial MIND Diet Scores demonstrated less growth in scores across the three visits (-.020) compared to those with lower initial MIND Diet Scores.

Table 16*Theoretical Executive Functioning Initial Structural Model Unstandardized Regression Weights*

Outcome	Pathway	Predictor	Estimate	Standard Error	P value
TEF Intercept	<----	Gender	.086	.039	.025*
TEF Intercept	<----	APOE Risk Score	-.072	.036	.049*
TEF Intercept	<----	MIND Score Visit 4	.026	.021	.216
TEF Intercept	<----	Age at Visit 4	-.064	.004	<.001**
TEF Slope	<----	Gender	.005	.008	.512
TEF Slope	<----	APOE Risk Score	-.005	.007	.516
TEF Slope	<----	MIND Score Visit 4	-.020	.007	.003**
TEF Slope	<----	Age at Visit 4	-.003	.001	<.001**

Note. $N = 1685$. $\chi^2(13) = 41.43$, $p = .000$ (TLI = .97; CFI = .99; RMSEA = .04). Table corresponds with Figure C3. $p \leq .01$ **; $p \leq .05$ *. TEF = Theoretical Executive Functioning.

8.4.2.4 Theoretical Executive Functioning Moderation Model

Given that the initial structural model of TEF was the only model to find a significant effect of MIND Diet Sum on TEF change over time, an additional analysis was conducted to determine whether APOE risk moderates the relationship between MIND Diet and TEF. An interaction variable APOE risk score x MIND Diet Sum at Visit 4 was added to the model (Figure C4, Appendix C). Goodness-of-fit statistics revealed adequate model fit, $\chi^2(18) = 67.22$, $p = .000$ (TLI = .96; CFI = .98; RMSEA = .04; AIC = 119.22). The statistically significant chi-square value was not necessarily surprising, given the sensitivity of the test. Positive slope values indicated that TEF increased over time (.324).

Pathway analysis (Table 17) revealed that Gender continues to have positive effects on initial TEF (.381), but not growth over time, suggesting that females tended to score higher on the TEF composite (.381 points higher) compared to males at the initial visit. Age at Visit 4 continues to have statistically significant negative effects on both initial level (-.065) and growth in TEF (-.003). This finding suggests that participants who were older at the initial visit show less change from one visit to the next compared to younger participants (-.003). Similarly, APOE risk score had significant effects on initial TEF (-.079), but not TEF growth over time, suggesting participants with higher APOE risk scores had lower TEF composite scores at Visit 4. MIND Diet Score at Visit 4 had significant negative effects on TEF growth over time (-.019). In other words, participants with higher initial MIND Diet Scores demonstrated less growth in TEF over time. Examination of the interaction variable indicated no significant effects on initial TEF (-.027) or growth over time (.014), suggesting no moderating effect.

Table 17*Theoretical Executive Functioning Moderation Structural Model Unstandardized Regression**Weights*

Outcome	Pathway	Predictor	Estimate	Standard Error	P value
TEF Intercept	<----	Gender	.381	.051	<.001**
TEF Intercept	<----	APOE Risk Score	-.079	.036	.028*
TEF Intercept	<----	MIND Score Visit 4	.014	.021	.516
TEF Intercept	<----	Age at Visit 4	-.065	.004	<.001**
TEF Intercept	<----	APOE x MIND Diet	-.027	.044	.548
TEF Slope	<----	Gender	-.006	.010	.560
TEF Slope	<----	APOE Risk Score	-.005	.007	.518
TEF Slope	<----	MIND Score Visit 4	-.019	.007	.004**
TEF Slope	<----	Age at Visit 4	-.003	.001	<.001**
TEF Slope	<----	APOE x MIND Diet	.014	.014	.330

Note. $N = 1683$. $\chi^2(18) = 67.22$, $p = .000$ (TLI = .96; CFI = .98; RMSEA = .04). Table corresponds with Figure C4. $p \leq .01$ **; $p \leq .05$ *. TEF= Theoretical Executive Functioning.

CHAPTER 9

DISCUSSION

The goal of the current dissertation was to investigate the longitudinal effects of MIND diet consumption and a metric for physical health on cognition, and furthermore, to determine whether APOE risk moderates the relationship between diet and cognitive performance longitudinally. The MIND diet emphasizes dietary components have been associated with neuroprotective and anti-inflammatory mechanisms, as well as reduced dementia risk. Components include green leafy vegetables and other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine. Importantly, however, the literature examining MIND diet adherence and cognitive performance longitudinally is lacking and there is currently not enough evidence to conclude causal relationships among hypothesized mechanisms (i.e., neuroprotection). APOE genotype is one of the most well-established genetic risk factors for LO-SAD; however, as noted previously, possessing the APOE e-4 allele does not necessarily lead to the clinical phenotype of AD. There remain several unanswered questions about how APOE genotype interacts with modifiable and nonmodifiable risk factors. As such, the current dissertation aimed to examine the direct relationships between nonmodifiable risk factors (age, gender, APOE genotype) and modifiable risk factors (MIND diet adherence and WHR) on cognition longitudinally, while also examining the potential interaction effect of APOE genotype and MIND diet adherence.

The current dissertation had three aims: to examine the longitudinal relationship between MIND diet adherence (Aim 1), physical health, in this case WHR (Aim 2), and APOE risk (Aim 3) on cognition; furthermore, to assess the potential moderating effect of APOE and MIND diet on cognition (Aim 3). Cognitive domains included previously established WRAP composite and

factor scores including TIM, TDM, TEF, EIM, ESR, and ESF. As mentioned in the *Methods and Materials* section, previously established cognitive outcomes were selected for two primary reasons: (1) to eliminate redundant factor analysis; (2) neuropsychological patterns of AD are consistent with disruptions in initial impairments in memory and verbal abilities, with mild-moderate impairments in problem-solving, cognitive flexibility, and conceptualization (i.e., executive functioning). Because aims were examined across several SEM models, key findings from the SEM models will be synthesized and discussed independently. Relevant aims will be identified when appropriate.

Initial nonparametric correlations revealed expected and unexpected associations. As expected, WHR was negatively correlated with MIND diet adherence along with all other cognitive outcomes, suggesting a lower WHR is associated with greater MIND diet adherence and better cognition. Unexpectedly, APOE risk score was not significantly associated with gender or cognition. There are several studies that suggest an interaction between sex/gender and APOE carrier status (Beydoun et al., 2012; Bretsky et al., 1999; Corder et al., 1995; Farrer et al., 1997; Neu et al., 2017; Payami et al., 1996; Riedel et al., 2016; Zhu et al., 2021). In fact, several studies suggest that heterozygous APOE e-4 status is associated with greater risk in the development of AD in women compared to men (Altmann et al., 2014; Beydoun et al., 2012; Neu et al., 2017; Payami et al., 1994) and additional research suggests women that are of homozygous APOE e-4 status are at increased risk for AD (Altmann et al., 2014; Breitner et al., 1999). In the current study, APOE risk was negatively associated with age. The negative association between age and APOE risk is a bit surprising, given that APOE risk is more predictive of LO-SAD. Considering the current sample was mostly female, and that research

suggests that the unique risk of APOE for men emerges earlier in the aging process (Riedel et al., 2016), it is possible that the nature of the sample is yielding unexpected associations.

Examination of initial hypothesized models revealed the theoretically derived composite score LGC models fit the data better, compared to the derived cognitive factor scores model. Empirical factor scores included items that were guided by theoretical perspectives, but the loadings and factor structure were data driven and weighted accordingly (Koscik et al., 2014). To compute the theoretical composites, all scores were standardized upon cognitive composite creation where lower scores indicated worse performance (Jonaitis et al., 2019). There are significant advantages for using empirical models, including they are data driven; however, a common disadvantage of empirical models is that results do not always generalize to beyond the sample, and only represent existing relationships among the data. Of course, the goal of any research study is to gather enough data to where the sample is representative of the general population, but that is rarely the case and certainly not in this situation given the demographic discrepancies of race and gender in this sample. The fact that theoretical composites fit the data better potentially confirmed the limitations of empirical models in the current study.

9.1 Initial Structural Models

Initial structural models included theoretically derived composite scores as outcomes, and selected predictors (i.e., age, gender, APOE risk score, MIND diet score at Visit 4, and WHR). Results revealed all cognitive outcomes (TIM, TDM, and TEF) improved over time, as indicated by a positive slope. At the outset, this finding is relatively unexpected, as some aspects of cognition are expected to remain stable or decline in the context of normal aging or neurodegenerative process. For example, memory difficulty is often one of the first and/or major complaint among older adults. As summarized by Murman (2015), age-related memory changes

include changes in speed of processing, attention and working memory, as well as executive functioning. Age-related cognitive changes likely result from structural and functional changes within the brain including reductions in grey matter, particularly in the temporal lobes and the hippocampus (Raz et al., 2004). Unique to AD, however, appears to be early reductions in the entorhinal cortex of the hippocampus which serves as an information relay center facilitating memory function (Braak & Braak, 1996). White matter reductions, to a greater extent, are also observed in the aging brain (Giorgio et al., 2010; Salat et al., 1999) which can contribute to age-associated memory (Rogalski et al., 2012) and executive functioning changes (O'Sullivan et al., 2001).

It is important to note, however, that improvement in cognition over time is not necessarily a surprising finding and other researchers have found a similar finding when assessing cognitive performance longitudinally. For example, MacAulay et al. (2018) found that memory and language improved on average over time in normal aging adults. To understand this finding, it is important to consider the biases inherent to longitudinal studies. Longitudinal studies are subject to attrition and therefore, participants who remain enrolled over time may be healthier, better educated, wealthier, and have higher cognitive scores at baseline (Van Beijsterveldt et al., 2002). Furthermore, cognitive performance is susceptible to practice effects as participants are often required to repeat the same tests multiple times, mostly across multiple time points, and may improve or maintain test scores despite the presence of cognitive decline (Abner et al., 2012; Salthouse, 2010). The magnitude of practice effects tends to be larger at younger ages (Salthouse, 2010), and therefore, a relevant consideration for the current study given the middle-age sample. Some cognitive tasks, such executive functioning or delayed memory tasks, rely on task novelty. For example, the Wisconsin Card Sorting Task relies on

novel problem solving, but a subject understanding the nature of the task due to repeated administration at the outset would have an advantage. This advantage could lead to less learning trials to the obtaining the first correct category sort or more category sorts. Overall, the improvement in cognitive composite scores across time should be considered in the context of biases inherent to longitudinal studies. Although the mean age only ranged from 63-68 years between V4 and V6, the age range at each visit remained steady at 34 years. Therefore, examining the cognitive composite scores while stratifying by age at each visit may provide more insight into the true relationships among predictor and outcome variables.

Results from initial structural models revealed gender had direct effects on initial TIM, TDM, and TEF scores, suggesting that in all cases, females tended to score higher on the three cognitive composites at the initial visit compared to males. This finding is consistent with the broader literature, suggesting women generally perform higher on baseline cognitive measures of global functioning, executive functioning, and memory (Levine et al., 2021; Li et al., 2017; McCarrey et al., 2016). In addition, the current study demonstrated women had higher scores on TIM and TDM over time, but not TEF. The existing literature suggests that women decline faster over time in global cognition and executive functioning, whereas men and women have similar declines in memory (Levine et al., 2021). However, it is possible the current study did not find a similar relationship that of Levine and colleagues (2021) because cognitive scores improved (as indicated by positive slope) over time, rather than declined. This current finding is also consistent with research suggesting that women may have greater cognitive reserve compared to men (Levine et al., 2021). Reserve, in general, is defined as the accumulation of neurocognitive resources across the lifespan that facilitate preservation of cognition in the context of age or neuropathology (Barulli & Stern, 2013; Stern, 2002, 2009; Stern et al., 2020). Cognitive reserve

more specifically are factors, such as cognitive, social, or physically rich experiences across the lifespan that preserve brain function and cognitive performance (Barulli & Stern, 2013; Stern, 2002, 2009; Stern et al., 2020). Factors that contribute to cognitive reserve include, but are not limited to, educational attainment and occupational complexity (Baldivia et al., 2008). According to Stern's model of cognitive reserve (Stern et al., 2020), these factors are generally protective against AD; however, individuals with higher cognitive reserve may demonstrate faster rates of decline due to accumulation of neuropathological changes despite anatomical compensatory mechanisms. Taken together, there remain several unanswered questions in understanding the sex-specific factors/patterns of change in AD and continues to be a direction of future studies.

Further examination of direct effects revealed that APOE risk and MIND diet scores had minimal effects on TIM and TDM outcomes (Aim 3). In contrast, APOE risk had significant effects on initial TEF, suggesting participants with higher APOE risk scores had significantly lower TEF composite scores at V4, compared to individuals with lower APOE risk scores. This finding supports existing research suggesting those with greater APOE risk (i.e., carrying an APOE-e4 allele) may be cognitively disadvantaged, or lower, at baseline (Carrasquillo et al., 2015); however, this finding has been noted in an older adult sample and research examining this finding in middle-age groups is limited.

Notably, APOE risk was not associated with worsening cognitive performance, longitudinally (Aim 3). Research characterizing the effect of APOE status on cognition is mixed. On one hand, some research suggests that APOE-e4 carrier status is associated with stable MCI without dementia progression in a population-based sample (Ganguli et al., 2019), or very little APOE-e4 related changes in cognition in samples of older adults (Batterham et al., 2012; Bondi et al., 1999; Bunce et al., 2004; Deary et al., 2003). In contrast, some research suggests greater

decline in APOE-e4 carriers (Bretsky et al., 2003; Caselli et al., 2011; Caselli et al., 2009; Deary et al., 2002; Packard et al., 2007; Schiepers et al., 2012) and possession of the APOE-e4 allele is associated with an increased rate of decline over five years in older adults (Carrasquillo et al., 2015). Some research questions whether there is a cognitive phenotype associated with APOE-e4 (Greenwood et al., 2005) or whether cognitive changes in those who possess the APOE-e4 allele and who are also demonstrating cognitive symptoms are in the preclinical stage of disease (have an underlying or undetected disease). Furthermore, research examining cognition and APOE status across the age spectrum suggests that when clinical dementia pathology is absent, APOE-e2 and e4 alleles do not exhibit antagonistic pleiotropy, where one trait is beneficial for cognition (i.e., APOE-e2) and one trait is detrimental for cognition over time (i.e., APOE-e4) (Bunce et al., 2014). Given the mean age for the WRAP sample was in the middle age range until the 6th visit and cognitively impaired individuals were excluded from data analysis, it is possible that we are capturing a lower APOE risk group. More specifically, a group where a clinical dementia pathology is absent and therefore, cognitive changes were not observable.

The understanding of APOE risk scores (calculated according to the natural logarithm of the odds ratio of e2/e3/e4 genotype) is important for interpreting the absence of APOE direct effects on longitudinal cognitive performance in the current study. Polygenic risk scores (PRSs) are commonly used in genome-wide association studies (GWAS) to determine disease risk based on genes/DNA. Some research suggests PRSs that include APOE are often driven by its inclusion and may be adequate in predicting change in cognitive function (Darst et al., 2017). Notably, however, APOE risk scores have their own set of limitations. As mentioned previously, the WRAP APOE risk score was calculated according to the odds ratio of e2/e3/e4 genotype as indicated in the meta-analysis of APOE genotype frequencies from the AlzGene. These odd

ratios were based on studies of white/Caucasian individuals and were calculated using the e2/e2 genotype as reference. The AlzGene database has not been updated since 2015. Although the current dissertation utilized data from the WRAP which yielded a sample of primarily white/Caucasian individuals (consistent with the AlzGene research database), the literature does suggest APOE allele status has differential effects depending on race as it pertains to AD risk (Dhana et al., 2022; Kuller et al., 1998). For example, although the presence of the e4 allele appears to be more likely in black/African American populations (Evans et al., 2003; Rajan et al., 2017), some research suggests the possession of the e4 allele does not necessarily increase risk for black/African Americans (Evans et al., 2003; Tang et al., 1998; Weuve, Barnes, et al., 2018). In addition, APOE and other PRS fail to consider dimensional risk factors associated with dementia risk, such as health disparities among ethnoracial groups. Regarding APOE risk more generally, in clinical risk studies, odds ratios have been shown to overestimate risk for APOE e2/e2 individuals and underestimate risk for APOE e4/e4 individuals (Reiman et al., 2020). Deming and colleagues (2023) recently suggested a neuropathology weighted APOE risk score may be better at accounting for APOE when predicting AD risk (Deming et al., 2023). Therefore, it is important to acknowledge that APOE risk scores, including the APOE risk score used in the current study, may have inherent bias in calculating risk for cognitive decline and/or disease onset, especially in non-white ethnoracial groups.

Although MIND diet adherence had no direct effect on TEF at the initial visit, MIND diet total scores had significant negative effects on TEF growth over time, suggesting those with higher initial MIND diet scores demonstrated less cognitive growth compared to those with lower initial MIND diet scores (Aim 1); however, examination of average MIND diet scores across time revealed limited variability (see Tables A2, A4, A6, Appendix A). This overall

finding was unexpected for several reasons. First, it was predicted that cognition would remain stable or decrease over time. Rather, the slope in initial TEF structural model was positive and therefore, suggests improvements in executive functioning. In contrast to theories of aging, such as Inhibition Theory (Hasher et al., 1991; Hasher & Zacks, 1988) or the Processing Speed Theory of Aging (Salthouse, 1985; Salthouse, 1996), abilities that are considered executive functioning, such as attention and processing speed tend to decline with older age. When the direct effect on MIND diet scores is considered in this context (i.e., those with higher initial MIND diet scores demonstrated less growth over time), it may be suggestive that those utilizing the MIND diet at V4 remained cognitively stable over time. In fact, findings from Mueller and colleagues (2020) suggest higher MIND diet scores may be associated with slower decline in executive dysfunction in a middle-age sample (mean age at baseline = 53.7 years, SD = 6.6 years). Furthermore, high adherence to the components of the MIND diet have been associated with improved cognition. For example, a randomized study conducted in 2018 by Assmann and colleagues revealed long-term nutritional doses of ALA to be associated with better cognitive functioning in early midlife. Studies examining DHA and EPA supplementation have been shown to lead to improvements in cognition in MCI (Ajith, 2018; Yurko-Mauro, 2010). Micronutrients, such as polyphenols, that are commonly found in fruits, vegetables, and whole grains have been associated with 47% reduced risk for global cognitive decline or a three-year period in older adults (Rabassa et al., 2015). Additionally, carotenoid-rich diets have been positively correlated with cognitive functioning in domains of episodic memory, semantic fluency, working memory, and executive functioning (Kesse-Guyot et al., 2014). The mechanisms for which the MIND diet and its components are hypothesized to be beneficial include anti-inflammatory, neuroprotection, and vascular benefits (Belkouch et al., 2016;

Cunnane et al., 2009; Latour et al., 2013). On the other hand, study findings also suggest that those with lower initial MIND diet scores demonstrated more growth in TEF over time. Notably, cognitive scores across time remained in the average range, consistent with what would be expected in a sample of cognitively unimpaired middle-aged adults. Although the reason for and rate of growth remains unclear, this finding may suggest individuals who have lower cognitive scores at baseline, even if still in the normal range, may experience greater cognitive benefits from intervention and warrants further investigation.

Existing research has attempted to examine MIND diet protective effects as it pertains to cognition. A recent longitudinal study found that greater MIND diet adherence was associated with reduced risk of developing MCI at 7-year follow-up (de Crom et al., 2022) and authors found a similar finding at a second follow-up of 5.9 years (de Crom et al., 2022). Notably, MIND diet adherence was slightly better at the second follow-up, suggesting that greater adherence may be associated with greater risk reduction. Similarly, greater MIND diet adherence was associated with better global cognitive functioning proximate to death (age at death = 90.8 years, SD = 61) (Dhana et al., 2021). At first glance, findings from the current study appear inconsistent with the current literature; however, in both studies (de Crom et al., 2022; Dhana et al., 2021) participants were older. For example, the mean age for participants in de Crom and colleagues (2022) was 67.7 years (SD = 7.8 years) and 75.3 years (SD = 5.9 years) at the first and second baseline, respectively. Overall, it is possible that the neuroprotective nature of greater MIND diet adherence could not be captured in a middle-age sample due to the restrictive range of cognitive scores and due to short follow-up duration, a limitation of observational studies highlighted by de Crom and colleagues (2022).

9.2 Moderation Model

An additional analysis was conducted to address Aim 3 and determine whether APOE risk moderated the relationship between MIND diet adherence and TEF. An interaction variable, “APOE risk score x MIND Diet Sum at Visit 4”, was added as a predictor to the model. Like the initial TEF structural model, participants with higher APOE risk scores had lower TEF composite scores at V4, again suggesting that higher APOE risk was associated with lower executive baseline functioning. Furthermore, those with higher initial MIND diet scores demonstrated less growth over time. Importantly, the interaction variable did not have significant effects on TEF, suggesting no moderating effect of APOE. Existing research examining the interaction effect of APOE and MIND diet is limited. As summarized by Yassine and Finch (2020), there are several animal studies that suggest APOE e4 carriers had 40% less omega-3 in their brains and are more vulnerable to omega-3 deficiency compared to noncarriers. This finding has been confirmed in human studies, as well (Yassine et al., 2017). Cross-sectionally, post-mortem assessment of APOE-e4 carriers who consumed at least 1 seafood meal per week (consuming more long-chain omega-3 fatty acids) had less AD neuropathology (Morris et al., 2016). Understanding this effect as it relates to cognition, particularly as a protective factor against cognitive decline, remains a crucial gap in the literature and is one of many resulting future directions from the current study.

9.3 Physical Health and Cognition

The goal of Aim 2 was to characterize the relationship between physical health, more specifically WHR, and cognition longitudinally. During the phase of fitting initial structural models to the data, model fit was significantly worse across all cognitive outcomes (TIM, TDM,

TEF) when WHR was included as a predictor. Adding an objective measure to the model accounted for the covariance of physical health measures and addressed an important study limitation that was highlighted by Mueller et al., 2020, as they did not account for the shared variance between diet and physical health. Many studies include BMI as an objective measure of physical health (Liu et al., 2021; Naqvi et al., 2011; Oleson et al., 2020). As mentioned previously, WHR was selected as an objective measure of physical health over BMI, given BMI's reliance on excess weight rather than excess fat. Unfortunately, to improve model fit, this variable was removed from the structural models, and therefore, the direct effect of physical health and cognition could not be characterized.

Importantly, the relationship between WHR and cognition was examined cross-sectionally using nonparametric correlations across each visit. As expected, WHR was negatively correlated with all cognitive domains at each visit, suggesting that lower WHR was associated with better cognitive performance. The cross-sectional nature of this relationship is consistent with the literature. An increase in WHR from ages 40-79 has been associated with impaired executive functioning and increased white matter hyperintensities in a longitudinal cohort enrolled in the Framingham Heart Study (Zade et al., 2013). Similarly, in a sample of midlife adults, higher WHR was associated with deficits in executive functioning and episodic memory (Hartanto & Yong, 2018). This effect remained consistent even when demographics, comorbid health issues, other health behaviors, personality, and self-perceived obesity were considered; however, Hartanto and Yong (2018) were unable to characterize the covariance between WHR and dietary habits. The shared variance between health factors like MIND diet adherence and WHR are important to consider, especially because WHR was negatively correlated with MIND diet adherence across all visits in the current study (lower WHR is

significantly associated with higher MIND diet adherence). Future studies should continue working toward separating the variance associated with different health factors to become more precise in the ability to predict cognitive change.

9.4 Limitations and Future Directions

The current study has several limitations. First, although the WRAP dataset is large, it is primarily a white, female, and well-educated sample. There remain substantial gaps in the scientific literature regarding ethnic and racial factors on AD risk (Babulal et al., 2019). Babulal and colleagues (2019) suggest that very little research has assessed how the following differ in racially and ethnic diverse groups: cognitive reserve, resilience/resistance to pathology, baseline brain health, the influence of linguistic/educational/cultural factors, neuroimaging and fluid-based biomarkers, neurodegeneration, and various cultural factors related to intervention benefits. Therefore, assessing these relationships in a diverse sample remains a goal for future research and will facilitate the generalizability of research findings.

9.4.1 Dietary Research

Dietary research is incredibly difficult to conduct. Despite the proposal of numerous hypothetical mechanisms as it pertains to brain health (e.g., neuroprotective, anti-inflammatory), they remain at this point, hypothetical. Interventional research designs manipulate variables within the study and are ideal for assessing causative relationships. Unfortunately, interventional research examining the relationship between diet and cognition commonly examine nutritional components (e.g., supplementation), rather than whole diet. Whole diet assessment, such as MIND diet total adherence, is important because foods contain specific nutrient/molecules that can facilitate absorption or production of other nutrients for energy. For example, antioxidants

facilitate the production of cysteine, which is pertinent for maintaining the body's homocysteine levels, and dietary fatty acids facilitate the absorption of carotenoids and other vitamins. Despite differential underlying theoretical mechanisms among the various whole diets (DASH, MIND, MD, KD), they are associated with beneficial effects on cognition. For example, a recent review comparing the influence of MD and KD on cognition suggests that both have sufficient evidence for reducing risk for cognitive decline based on prospective cohort studies, randomized controlled trials, along with cross-sectional and longitudinal studies (Vinciguerra et al., 2020). Importantly, the MIND diet appears to provide greater protection against cognitive decline compared to other diets (DASH and MD diet alone) in observational studies (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015). Therefore, research assessing the combination of foods and nutrients as a whole diet may provide additional evidence for how dietary components interact together to provide additional health benefits.

The current study demonstrated a strength in this regard, assessing total MIND diet adherence, calculated by the various dietary components. Importantly, the WRAP used an adapted MIND diet questionnaire (see *Materials and Methods* section) which may prevent direct comparison to other studies who did not use the adaptive version; however, several studies have examined MIND diet adherence and its relationship with cognition and physical health. In the current study, the average MIND diet sum was relatively consistent across timepoints (V4 $M = 9.22$, V5 $M = 9.41$, V6 $M = 9.40$, SDs = 1.95, 1.86, and 1.92 respectively) which confirms dietary habits remained consistent across time for participants. Compared to other studies who the MIND diet, MIND diet scores were less than 1 SD higher than other samples. For example, in a subset of participants without dementia from the Rush Memory and Aging Project, the mean MIND diet sum was 7.4 (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015). In a subset of

participants with AD from the same project, the average MIND diet sum also was 7.4 (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015) and similarly, the average MIND diet score was 7.4 ($SD = 1.6$) for a population-based sample (2009-2012) in the Netherlands (de Crom et al., 2022). According to a recent systematic review by Kheirouri and Alizadeh (2022) that included studies examining the relationship between MIND diet adherence (mostly assessed by some version of the FFQ) and cognition in older adults at various time points, the average MIND diet scores were variable and ranged from 4.9 (Berendsen et al., 2018) to 9.6 (Morris, Tangney, Wang, Sacks, Bennett, et al., 2015). Overall, the current study demonstrated MIND diet scores are generally comparable, if not slightly higher, than the average MIND diet scores across samples; however, scores are highly variable depending on the sample and therefore, continues to warrant future investigation.

Unfortunately, analyzing whole diet consumption also limits the assessment and characterization of specific macro- and micronutrients. There is existing literature that examines the relationship between dietary components, APOE genotype, and AD risk; however, research is somewhat mixed, and significant relationships depend on sample characteristics, measurement of cognitive functioning and dietary components, and study design. For example, some research suggests that fish and seafood consumption are uniquely important for cognitive health long-term. More specifically, consuming ≥ 1 serving of per week of fish has been associated with reduced risk for cognitive decline in adults who were APOE e4 carriers, but only in those who were ≥ 65 years old (Qin et al., 2014). Adults 55-64 years did not demonstrate an association between fish consumption and cognition (Qin et al., 2014). Additionally, higher nut intake in older women (≥ 5 times per week) was associated with modestly better cognitive performance over time (O'Brien et al., 2014) and high consumption of green leafy vegetables has been

associated with slower cognitive decline in epidemiological studies that included aging individuals (Kang et al., 2005; Morris et al., 2006). In contrast, higher fruit intake has been associated with reduced brain volume in lower temporal and hippocampal volumes (Gu et al., 2015), likely due to high glycemic index seen in several fruits. Furthermore, higher tofu intake, although high in PUFAs, has been associated with worse memory performance in older adults (Xu et al., 2015).

A continual challenge in nutrition and dietary research is obtaining reliable and accurate dietary data. Often, researchers rely on self-report to provide estimates of dietary foods and/or portions. Dietary recall requires individuals to assess their food and beverage consumption retrospectively (Gurinovic et al., 2016). Ideally, description of food items includes preparation methods, brand names, portion sizes, recipes, and contextual data (such as location and timing of meal consumption). Electronic methods have been developed that prompt the individual to report when they eat and allow for foods to be selected based on categories. Other options for dietary assessment include questionnaires, which allows researchers to avoid cumbersome reporting that is associated with in-the-moment dietary tracking and overreliance on an participants' memory for dietary recall. Common questionnaires include the FFQ (Shim et al., 2014) and the Nutrition and Health Questionnaire (NHQ) (Kaaks & Riboli, 1997; Riboli & Kaaks, 1997). Most questionnaires ask participants to estimate how often they consume certain foods (meat, fish, eggs, bread, cereal, fruit, etc.) and beverages, usually *per day* or *per week*. Unfortunately, not all dietary questionnaires include the necessary questions to accurately calculate specific diet adherence retrospectively. For example, the NHQ is limited in characterizing portion sizes and frequency of food/beverage consumption. As a result, many researchers opt to selecting questionnaires assessing specific diets, such as the MIND Diet Questionnaire. This forces

researchers to be limited in their dietary scope and they continue to remain susceptible to participant recall bias depending on the recall time frame. Overall, the field of dietary research would benefit from the development of additional valid and reliable dietary estimates.

9.4.2 APOE Risk Scores

As highlighted by Deming and colleagues (2023), there are several limitations associated with using APOE genetic risk for predicting AD-related outcomes: (1) APOE-e4 status and e4 allele count do not account for effects of reduced risk conferred by APOE-e2 (Reiman et al., 2020); (2) the allele count approach assumes that genetic risk of APOE-e4 is additive; (3) APOE-e4 status has limitations in statistical modeling such as loss of statistical power or problems with model convergence when treated as a categorical variable due to its low frequency (Koller & Stahel, 2017). One way research has addressed these limitations is calculating APOE risk scores and PRS. As mentioned previously, PRSs have been beneficial in examining the effects of genetic variance, even if small, in genome-wide association studies. When allele characterization is combined with other genetic variations in DNA, there is typically good prediction of disease presentation (International Schizophrenia et al., 2009; Wineinger et al., 2013). However, research examining the added benefit of considering AD-related pathology biomarkers in PRSs compared to biomarkers alone or allele presence is mixed. On one hand, in PRSs that include APOE genotype, APOE appears to be the driving factor of disease risk, further highlighting the importance of APOE risk on AD outcomes (Darst et al., 2017). Darst and colleagues (2017) also argued that pathway-specific risk scores (including biomarkers) are not necessarily more predictive than an overall PRS or APOE genotype (Darst et al., 2017). On the other hand, more recent research by Deming and colleagues (2023) suggests a neuropathology weighted APOE risk score is better at predicting CSF biomarkers. Notably, Deming and

colleagues (2023) did not examine the neuropathology weighted APOE risk score's ability to predict cognitive outcomes; however, in cognitively unimpaired participants, there was evidence the neuropathology weighted APOE risk score was adequate in predicting CSF biomarkers.

Darst and colleagues (2017) found that pathway-specific risk scores were not better at predicting AD-risk more broadly, compared to overall PRS and APOE genotype. Both overall PRS and APOE genotype were adequate predictors of AD-risk, but the amount of variance explained by PRSs (pathway specific, overall PRS, and APOE) was small (Darst et al., 2017). In relation to cognition, the largest variance accounted for across all risk scores was 0.2% suggesting poor ability to predict cognition (Darst et al., 2017).

It is clear, based on the literature, that APOE genotype, particularly the e4 allele is associated with higher risk of the development of AD. However, the literature examining APOE as a risk factor for cognitive decline and its interaction with other variables continues to be mixed. The mixed literature is likely partially accounted for by two main gaps in assessing genetic risk as it pertains to AD-related outcomes. First, establishing valid estimates of APOE risk and protective effects requires further investigation (e.g., risk scores). Second, the application of the various risk scores (e.g., overall PRS, APOE risk score, neuropathology-based risk scores) to predict cognitive trajectories remains understudied.

9.4.3 Sensitivity and Specificity of Cognitive Measures

Traditionally, neuropsychological tests have been considered sensitive (accurately diagnosing people with impairment) and specific (accurately diagnosing people without impairment) measures to capture cognitive changes among individuals. Undergoing a neuropsychological evaluation is considered the “gold-standard” for characterizing cognitive changes or current cognitive functioning as well as assessing progressing impairment over time.

As with other medical conditions, early diagnosis of MCI and/or AD is critical to anticipate future needs. In the case of MCI, early intervention strategies may be implemented to potentially delay or protect against future functional and cognitive declines. Furthermore, even those with AD may benefit from modifiable risk factor intervention studies, such as diet, to slow the progression of the neurodegenerative condition. Recently, however, the sensitivity of neuropsychological tests has come into question. More specifically, cognitive measures' ability to capture subtle cognitive changes that are clinically meaningful in cognitively unimpaired individuals, those with subjective cognitive concerns, or even those with MCI. The current study included a sample of middle-age, cognitively unimpaired adults and it is possible that traditional neuropsychological tests were not sensitive enough to capture change associated with the interested predictors (e.g., diet, genotype, etc.). Not only will more sensitive tests allow cognitive changes to be captured in a reliable and valid manner, but more sensitive test development may also assist with capturing practice effects versus true cognitive change.

Furthermore, cognitive outcomes included in the LGC models were previously established composite (theoretical) and factor scores (empirical), comprising of standardized values. Utilizing standardized cognitive outcomes removed external variance, such as variance related to age and education, so the models can capture clinically meaningful and significant change (i.e., variance above and beyond demographic variables). However, it is also possible that by using standardized outcomes and including demographic predictors in the model may have made it more difficult to capture change across time, as we are accounting for age and gender variance twice: first by standardizing cognitive outcomes and second, by including demographic predictors in the model.

Recently, the field of neuropsychology has shifted to examining process scores to capture subtle cognitive changes associated with subjective cognitive decline and MCI. Process scores are derived from neuropsychological tests and capture the number of errors, as well as *how* and *why* the individual achieved a specific total score on a specific measure (Kaplan, 1988). In fact, research suggests word-list process analysis can discriminate between amnesic MCI and early AD (Delis et al., 1994; Libon et al., 2011; Loewenstein et al., 2004; Salmon & Bondi, 2009; Welsh et al., 1991; Woodard et al., 1999). Recently, Thomas et al. (2018) suggested process scores may increase sensitivity for capturing subjective cognitive decline in older adults who would otherwise, be considered as having normal cognition. Because the current study used established composite and factor scores, process scores were not included in data analysis. Future studies should consider integrating process scores into predictive models, to capture subtle cognitive changes in cognitively normal individuals.

The field of cognitive measurement would benefit from additional research in the following areas: (1) the development and validation of additional cognitive measures that are more sensitive to changes in cognitively unimpaired or mildly impaired individuals; (2) include process scores in predictive models; (3) determine optimal time frames/statistical models to capture subtle cognitive changes across time; (4) use the same models in the current study and replace standardized cognitive outcomes with cognitive latent variables derived from raw data.

9.4.4 Sample Demographics

As previously noted, there are a limited number of studies that examine the relationship between MIND diet and cognition longitudinally in middle-age samples (Mueller et al., 2020). In contrast, there is more research assessing the longitudinal relationship between MIND diet and cognition in older adults (Dhana et al., 2021; Morris, Tangney, Wang, Sacks, Barnes, et al.,

2015). A recent systematic review (Kheirouri & Alizadeh, 2022) highlighted six articles that examined the longitudinal relationship between MIND diet and cognition in older adults (mean age ≥ 65) (Arjmand et al., 2022; Cherian et al., 2019; Morris, Tangney, Wang, Sacks, Barnes, et al., 2015; Morris, Tangney, Wang, Sacks, Bennett, et al., 2015; Munoz-Garcia et al., 2020; Shakersain et al., 2018). Morris and colleagues (2015) concluded that greater MIND diet adherence was associated with slower global cognitive decline in an older adult sample (average sample age = 81.4 years, SD 7.2 years), even when age, sex, education, total energy intake, APOE-e4 status, smoking, physical activity, and cognitive activity participation were accounted for. In fact, this finding was equivalent to being 7.5 years younger (Morris et al., 2016). Future research should aim to examine the effects of diet on cognition by conducting longitudinal and experiment/intervention studies. Although there are a handful of randomized controlled trials that have examined MIND diet and cognition, these studies typically included samples with physical health concerns, such as obesity (Arjmand et al., 2022) or vascular insult (Cherian et al., 2019), and provide a limited long-term follow-up (for example, a three-month follow-up in Arjmand et al., 2022). Recent research has acknowledged the need for intervention studies with long-term follow-up. Liu and colleagues (2021) are currently conducting a three-year randomized controlled trial to examine the effects of MIND diet on cognition in 604 individuals at risk for AD (65-84 years old). Results of the RCT are much anticipated and the study is an important step to better understand the causative relationships between MIND diet and brain/cognitive health.

Given that this sample is middle-aged, and the mean age did not surpass 65 (older adult range) until the 6th visit, it is possible that the relationships of interest were not captured by neuropsychological measures and/or individuals were not expressing behavioral representations

in the form of cognitive changes. Therefore, future research may include analyzing data across additional visits to expand the already limited range in cognitive scores that are associated with middle age. Furthermore, as noted previously, the WRAP data includes majority non-Hispanic white individuals (89%) which limits generalizability of the current findings to different ethnorracial groups. In addition to considering the inherent bias of APOE risk scores, and Uh therefore choosing a risk score that has been appropriately applied to non-white ethnorracial groups, it is recommended that the current study be replicated with more racially diverse samples. There are several datasets that include the assessment of cognition in more diverse samples, such as, but not limited to the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS), Baltimore Longitudinal Study on Aging (BSLA), National Alzheimer's Coordinating Center (NACC), or the Chicago Health and Aging Project (CHAP). According to a recent publication assessing bias in cognitive testing for older adults with sensory impairment, the ARIC-NCS includes 24% black/African American participants and the BLSA includes 34% of black/African American participants (Nichols et al., 2022). Similarly, a recent publication using the NACC dataset examining whether black/African American and non-Hispanic white differ in dementia, prevalence, risk factors, and presentation included 5,700 black/African American individuals across 39 Alzheimer's Disease Research Centers (Lennon et al., 2022). Lastly, Dhana and colleagues (2022) included 2,359 black/African American participants in their analysis of genetic risk, healthy lifestyle adherence, and cognitive decline. Importantly, dietary assessment may vary depending on the selected dataset. For example, the CHAP includes assessment of the MIND diet, whereas the BSLA dataset assesses individual dietary components (according to the data dictionary released in January 2018).

The current dissertation examined the relationships among modifiable and nonmodifiable risk factors and cognition longitudinally in an enriched sample of cognitively unimpaired individuals. As described previously, there may be limitations associated with including a sample of people who are cognitively unimpaired. There are several studies that have examined the relationship between MIND diet adherence and cognition in samples of older adults with MCI and/or dementia. SEM allows for the comparison of competing models using fit indices (if predictors and outcomes remain consistent across models). It is possible that the relationships among predictors and cognitive outcomes, as well as interaction effects, are significantly different by consensus group (*Cognitively Unimpaired, Stable; Cognitively Unimpaired, Declining; Impaired, not MCI; Clinical MCI; Dementia*). Therefore, future research may explore analyzing the predicted relationships across cognitively diverse samples.

9.5 Conclusions

Improving the understanding of causative relationships underlying hypothesized mechanisms of dietary benefits on cognition and AD risk is crucial to reduce the burden of AD within the individual, their families, and medical system. The current study did not find evidence suggesting that MIND diet adherence is associated with better cognitive outcome in middle-aged adults. Furthermore, results were not indicative of an interaction effect between APOE risk and MIND diet. The null findings, however, highlighted important gaps in the literature and areas that would benefit from additional investigation, including but not limited to, developing precise APOE risk scores, repeating the proposed models with ethnoracial and cognitively diverse samples, and examining the role of MIND diet dietary components in structural models.

CHAPTER 10**REFERENCES**

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APPENDICES

APPENDIX A

Table A1*Spearman's Rho Correlation Coefficients of Model Predictor and Outcome Variables*

	1	2	3	4	5	6	7	8	9	10	11
1. Age		-.02	.17	-.09**	.05*	-.18**	-.15**	-.41**	-.13**	-.08**	-.30**
2. Gender			-.60**	.05	.20	.04	.03	.16	.20**	-.06	.13**
3. WHR				-.17	-.18**	-.20**	-.19**	-.20**	-.20**	-.11**	-.15**
4. APOE Risk					-.05	-.07	-.09	-.00	-.03	-.11	.01
5. MIND Diet						.10**	.09**	.08**	.10**	.08**	.02
6. TIM Composite							.90**	.41**	.69**	.78**	.39**
7. TDM Composite								.37**	.56**	.77**	.35**
8. TEF Composite									.35**	.26**	.87**
9. EIM Factor										.42**	.31**
10. ESR Factor											.22**
11. ESF Factor											

Note. $p \leq .01$ ** (two-tailed); $p \leq .05$ * (two-tailed). WHR = waist-to-hip ratio, APOE = apolipoprotein, MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay, TIM= Theoretical Immediate Memory, TDM = Theoretical Delayed Memory, TEF = Theoretical Executive Functioning, EIM = Empirical Immediate Memory, ESR = Empirical Story Recall, ESF = Empirical Speeded Flexibility.

Table A2*Visit 4 Predictor and Outcome Characteristics: Means and Standard Deviations*

	<i>N (%)</i>	<i>M (SD)</i>
Age	1094	63.38 (6.40)
WHR	1050	0.87 (0.10)
MIND Diet Sum	473	9.22 (1.95)
Theoretical Immediate Memory Composite	1049	0.12 (1.01)
Theoretical Delayed Memory Composite	1047	0.17 (0.98)
Theoretical Executive Functioning Composite	1011	-0.11 (1.02)
Empirical Story Recall Factor	1051	0.07 (1.08)
Empirical Delayed Memory Factor	1051	0.02 (0.98)
Empirical Speeded Flexibility Factor	1013	0.13 (1.05)

Note. WHR = waist-to-hip ratio. Gender and APOE risk score remain unchanged from baseline and therefore, are not included in the table but remain predictors in the LGC model. Theoretical Composite Scores and Empirical Factor Scores are represented as z-scores.

Table A3*Visit 4 Spearman's Rho Correlation Coefficients of Model Predictors and Outcome Variables*

	1	2	3	4	5	6	7	8	9	10	11
1. Age		-.05	.15**	-.12**	.06	-.25**	-.23**	-.44**	-.23**	-.18**	-.43**
2. Gender			-.61	.05	.15**	.21**	.18**	.18**	.23**	.06*	.14**
3. WHR				-.05	-.22**	-.18**	-.18**	-.19**	-.20**	-.10**	-.12**
4. APOE Risk					.08	.01	.01	.01	.04	-.03	-.02
5. MIND Diet						.06	.04	.04	.08	.07	-.06
6. TIM Composite							.89**	.41**	.69**	.76**	.37**
7. TDM Composite								.36**	.57**	.76**	.32**
8. TEF Composite									.36**	.26**	.86**
9. EIM Factor										.41**	.31**
10. ESR Factor											.21**
11. ESF Factor											

Note. $p \leq .01$ ** (two-tailed); $p \leq .05$ * (two-tailed). WHR = waist-to-hip ratio, APOE = apolipoprotein, MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay, TIM= Theoretical Immediate Memory, TDM = Theoretical Delayed Memory, TEF = Theoretical Executive Functioning, EIM = Empirical Story Recall, ESR = Empirical Delayed Memory, ESF = Empirical Speeded Flexibility.

Table A4*Visit 5 Predictor and Outcome Characteristics: Means and Standard Deviations*

	<i>N (%)</i>	<i>M (SD)</i>
Age	862	65.80 (6.32)
WHR	820	0.87 (0.09)
MIND Diet Sum	838	9.41 (1.86)
Theoretical Immediate Memory Composite	814	0.29 (1.01)
Theoretical Delayed Memory Composite	813	0.29 (0.95)
Theoretical Executive Functioning Composite	770	-0.12 (0.98)
Empirical Story Recall Factor	822	0.22 (1.08)
Empirical Delayed Memory Factor	819	0.10 (0.98)
Empirical Speeded Flexibility Factor	771	0.28 (1.04)

Note. WHR = waist-to-hip ratio. Gender and APOE risk score remain unchanged from baseline and therefore, are not included in the table but remain predictors in the LGC model. Theoretical Composite Scores and Empirical Factor Scores are represented as z-scores.

Table A5*Visit 5 Spearman's Rho Correlation Coefficients of Model Predictors and Outcome Variables*

	1	2	3	4	5	6	7	8	9	10	11
1. Age		-.07*	.13**	-.15**	.05	-.26**	-.23**	-.46**	-.24**	-.11**	-.48**
2. Gender			-.66**	.05	.11**	.24**	.22**	.21**	.28**	.09**	.13**
3. WHR				-.07*	-.16**	-.19**	-.19**	-.19**	-.28**	-.10**	-.15**
4. APOE Risk					.05	-.01	.01	-.02	-.01	-.01	-.01
5. MIND Diet						.07	.05	.05	.07*	.05	.01
6. TIM Composite							.89**	.40**	.69**	.77**	.33**
7. TDM Composite								.36**	.56**	.76**	.29**
8. TEF Composite									.37**	.22**	.88**
9. EIM Factor										.41**	.31**
10. ESR Factor											.16**
11. ESF Factor											

Note. $p \leq .01$ ** (two-tailed); $p \leq .05$ * (two-tailed). WHR = waist-to-hip ratio, APOE = apolipoprotein, MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay, TIM= Theoretical Immediate Memory, TDM = Theoretical Delayed Memory, TEF = Theoretical Executive Functioning, EIM = Empirical Immediate Memory, ESR = Empirical Story Recall, ESF = Empirical Speeded Flexibility.

Table A6*Visit 6 Predictor and Outcome Characteristics: Means and Standard Deviations*

	<i>N (%)</i>	<i>M (SD)</i>
Age	497	68.03 (6.10)
WHR	467	0.88 (0.10)
MIND Diet Sum	480	9.40 (1.92)
Theoretical Immediate Memory Composite	463	0.35 (1.04)
Theoretical Delayed Memory Composite	463	0.36 (1.00)
Theoretical Executive Functioning Composite	408	-0.18 (1.07)
Empirical Immediate Memory Factor	477	0.25 (1.13)
Empirical Story Recall Factor	473	0.21 (1.01)
Empirical Speeded Flexibility Factor	408	0.25 (1.11)

Note. WHR = waist-to-hip ratio. Gender and APOE risk score remain unchanged from baseline and therefore, are not included in the table but remain predictors in the LGC model. Theoretical Composite Scores and Empirical Factor Scores are represented as z-scores.

Table A7*Visit 6 Spearman's Rho Correlation Coefficients of Model Predictors and Outcome Variables*

	1	2	3	4	5	6	7	8	9	10	11
1. Age		-.12**	.12**	-.16**	.04	-.30**	-.30**	-.50**	-.27**	-.17**	-.49**
2. Gender			-.67**	.05	.11*	.26**	.23**	.19**	.29**	.10*	.14**
3. WHR				-.06	-.16**	-.18**	-.17**	-.17**	-.21**	-.09	-.12*
4. APOE Risk					.05	.04	.05	.04	.02	-.03	.00
5. MIND Diet						.13**	.12**	.09	.08	.12*	.04
6. TIM Composite							.90**	.41**	.71**	.79**	.37**
7. TDM Composite								.37**	.60**	.77**	.33**
8. TEF Composite									.39**	.24**	.91**
9. EIM Factor										.47**	.36**
10. ESR Factor											.21**
11. ESF Factor											

Note. $p \leq .01$ ** (two-tailed); $p \leq .05$ * (two-tailed). WHR = waist-to-hip ratio, APOE = apolipoprotein, MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay, TIM= Theoretical Immediate Memory, TDM = Theoretical Delayed Memory, TEF = Theoretical Executive Functioning, EIM = Empirical Immediate Memory, ESR = Empirical Story Recall, ESF = Empirical Speeded Flexibility.

Table A8*Nonparametric Correlations of Cognitive Outcomes Across Visit 4, 5, and 6*

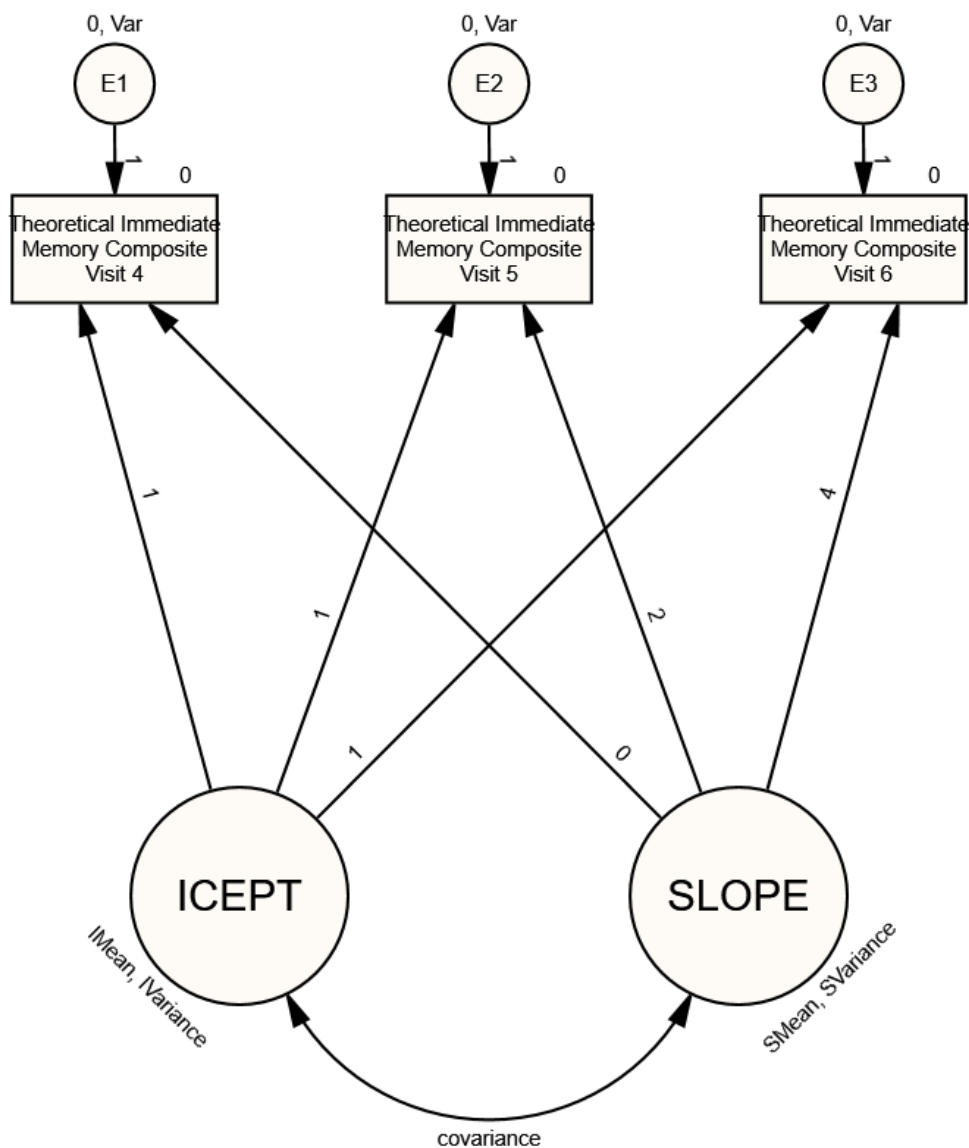
		Visit 4	Visit 5	Visit 6
TIM Composite	Visit 4		.78**	.75**
	Visit 5			.81**
	Visit 6			
TDM Composite	Visit 4		.76**	.78**
	Visit 5			.85**
	Visit 6			
TEF Composite	Visit 4		.90**	.88**
	Visit 5			.90**
	Visit 6			
EIM Factor	Visit 4		.57**	.57**
	Visit 5			.62**
	Visit 6			
ESR Factor	Visit 4		.70**	.79**
	Visit 5			.77**
	Visit 6			
ESF Factor	Visit 4		.81**	.80**
	Visit 5			.86**
	Visit 6			

Note. $p \leq .01$ **; $p \leq .05$ *. TIM= Theoretical Immediate Memory, TDM = Theoretical Delayed Memory, TEF = Theoretical Executive Functioning, EIM = Empirical Immediate Memory, ESR = Empirical Story Recall, ESF = Empirical Speeded Flexibility.

APPENDIX B

Figure B1

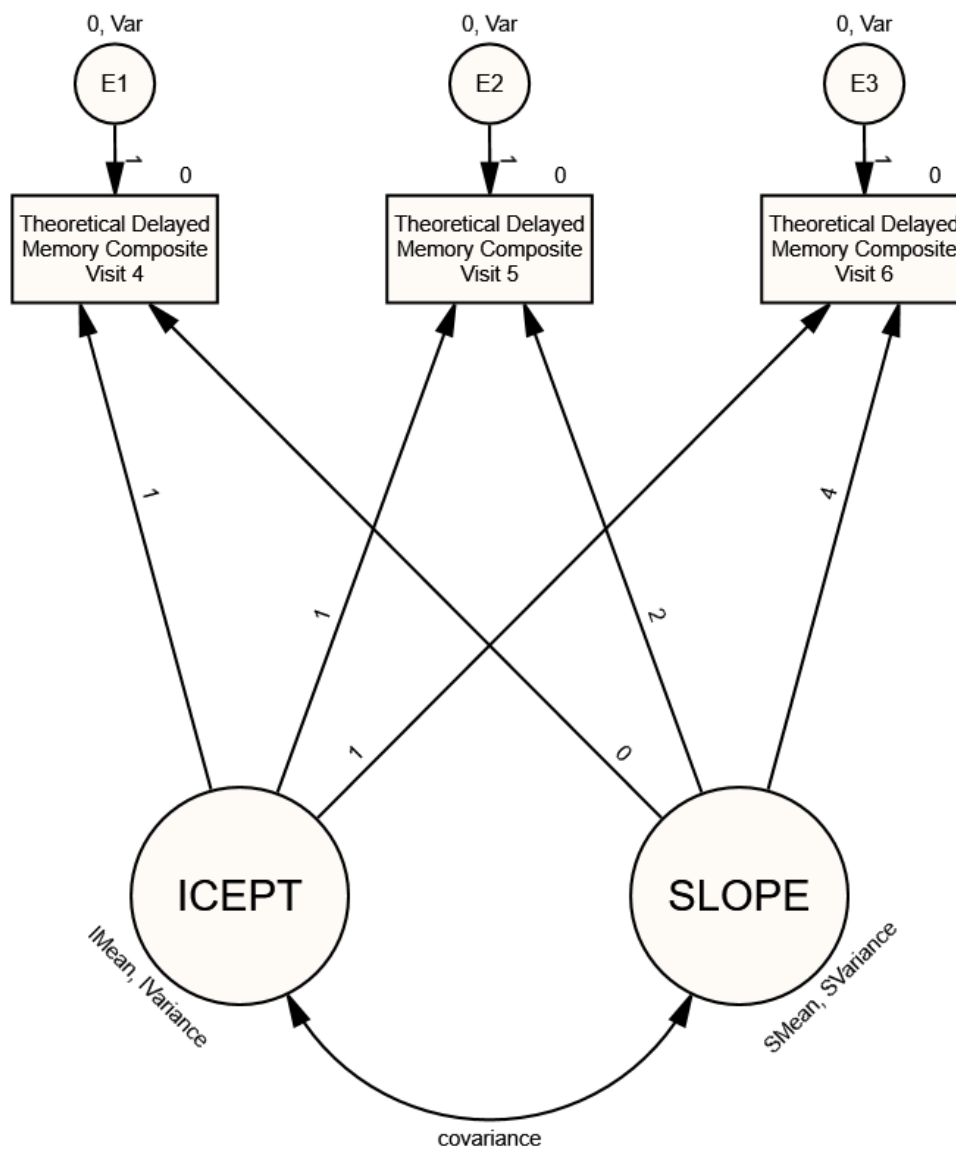
Theoretical Immediate Memory Composite Initial Hypothesized Model



Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

Figure B2

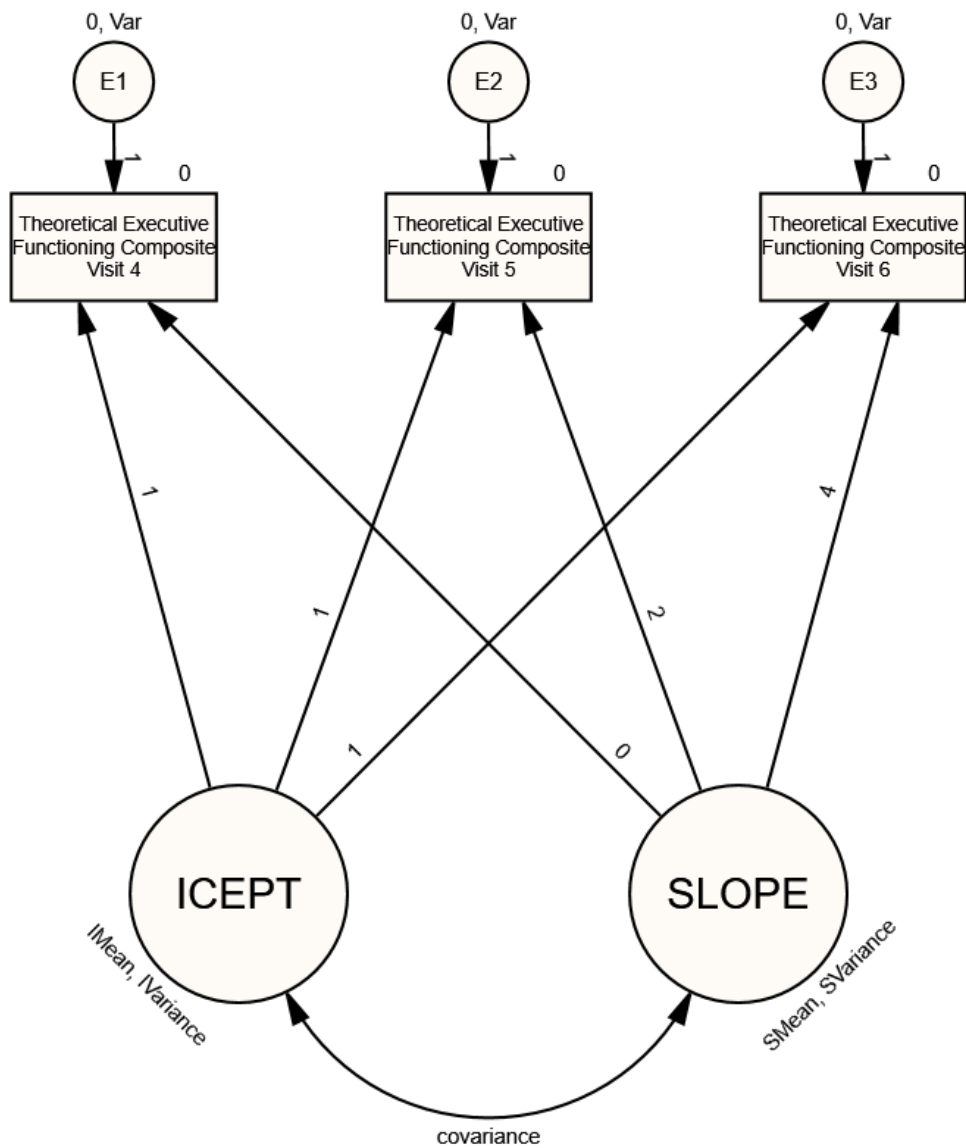
Theoretical Delayed Memory Composite Initial Hypothesized Model



Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

Figure B3

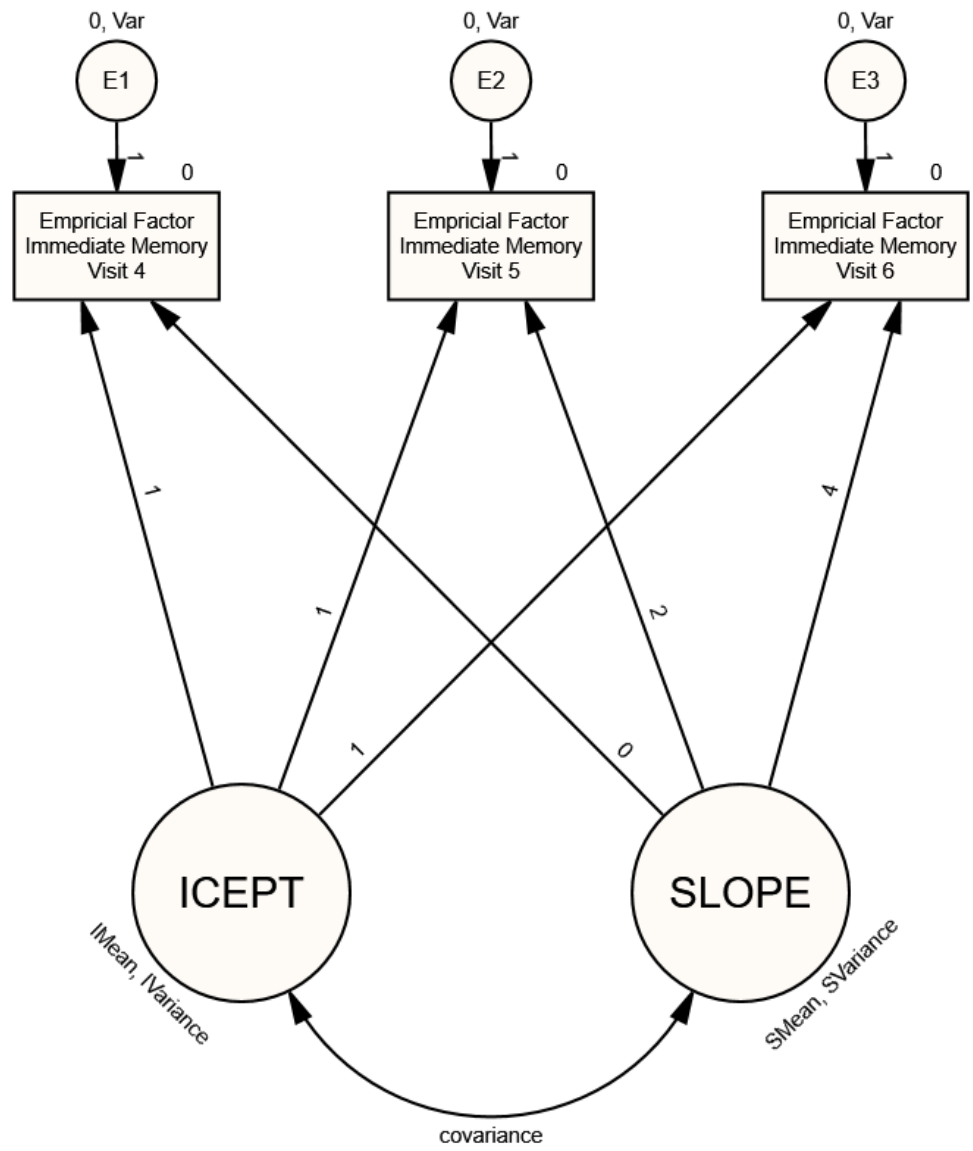
Theoretical Executive Functioning Composite Initial Hypothesized Model



Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

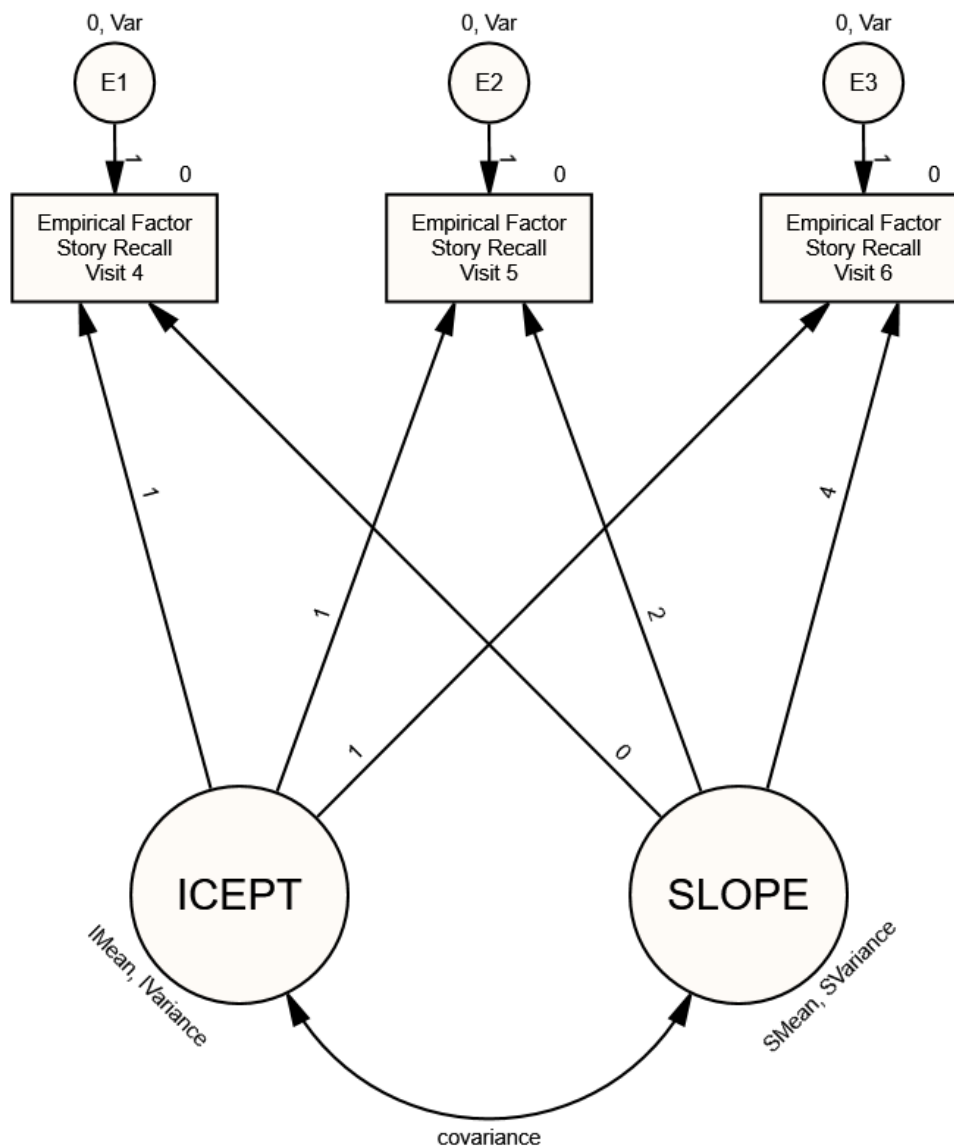
Figure B4

Empirical Immediate Memory Initial Hypothesized Model

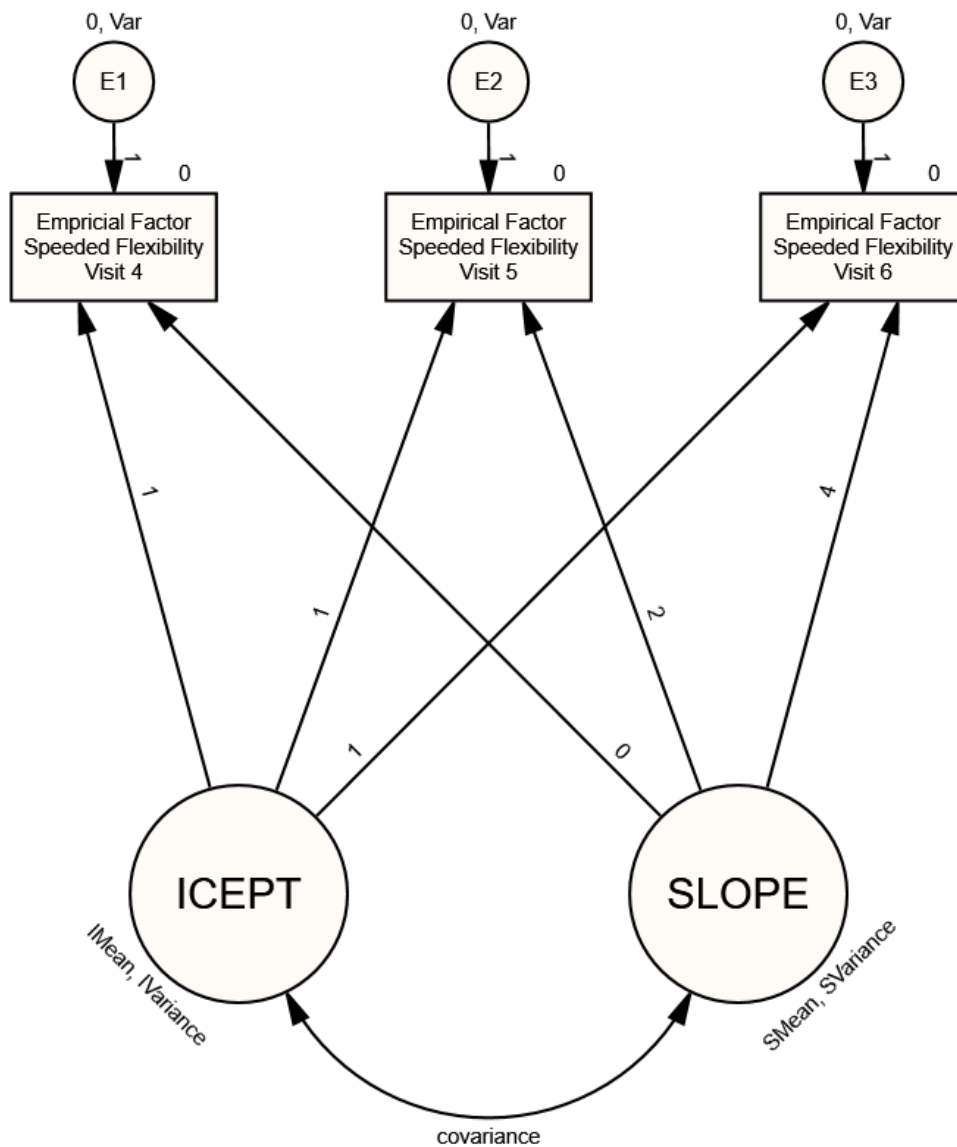


Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

Figure B5

Empirical Story Recall Factor Initial Hypothesized Model

Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

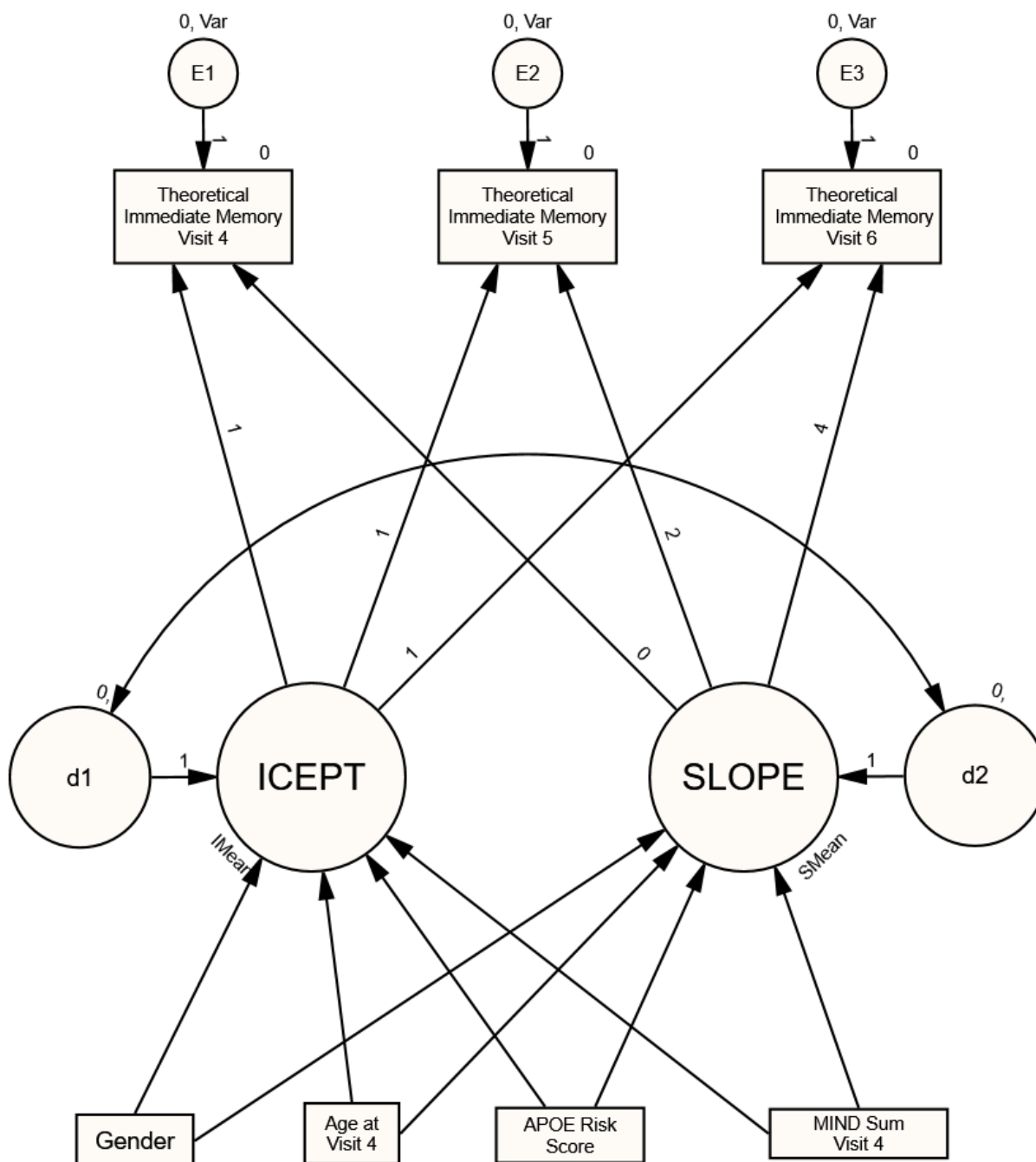
Figure B6*Empirical Speeded Flexibility Factor Initial Hypothesized Model*

Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

APPENDIX C

Figure C1

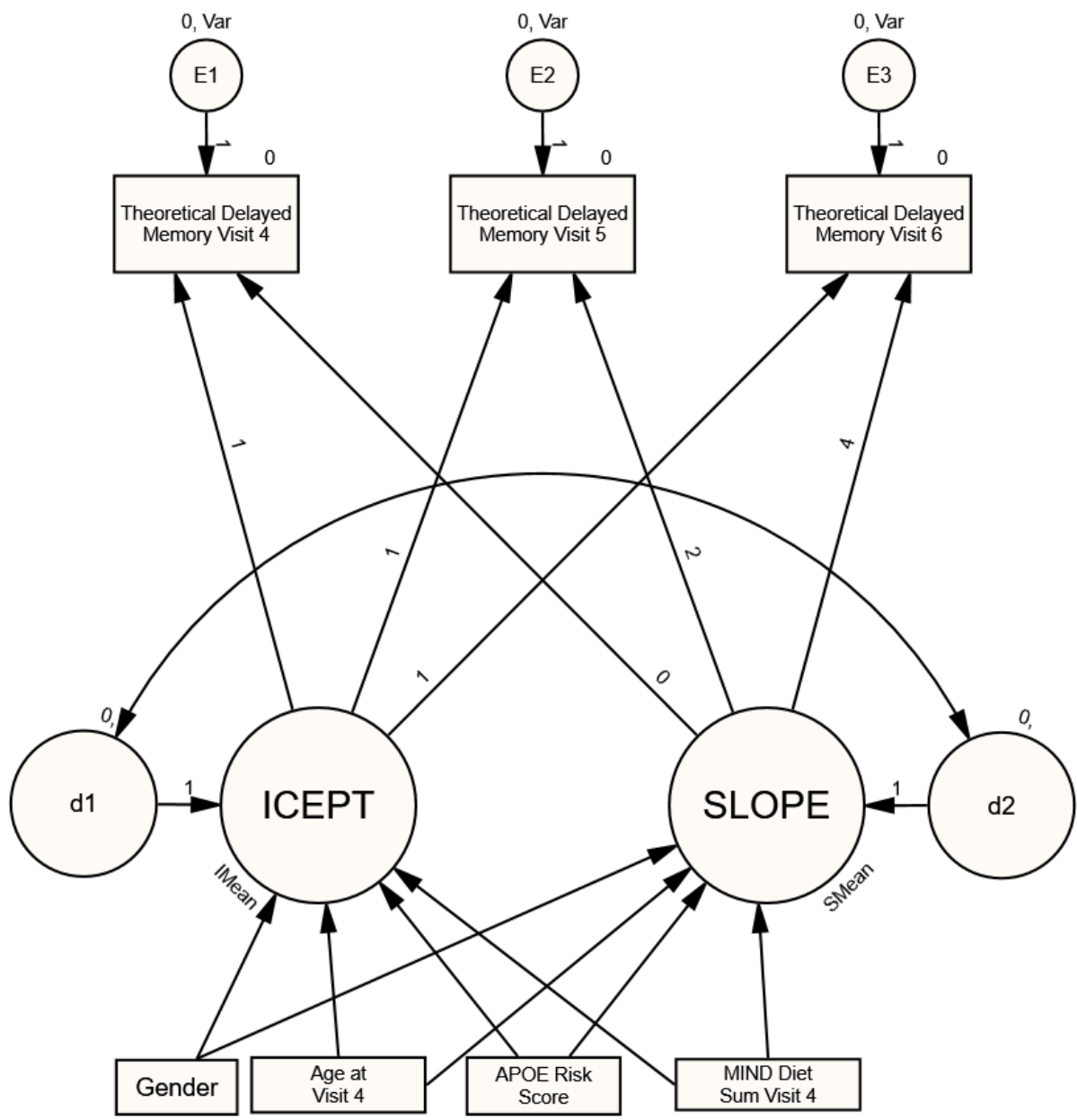
Theoretical Immediate Memory Composite Initial Structural Model



Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

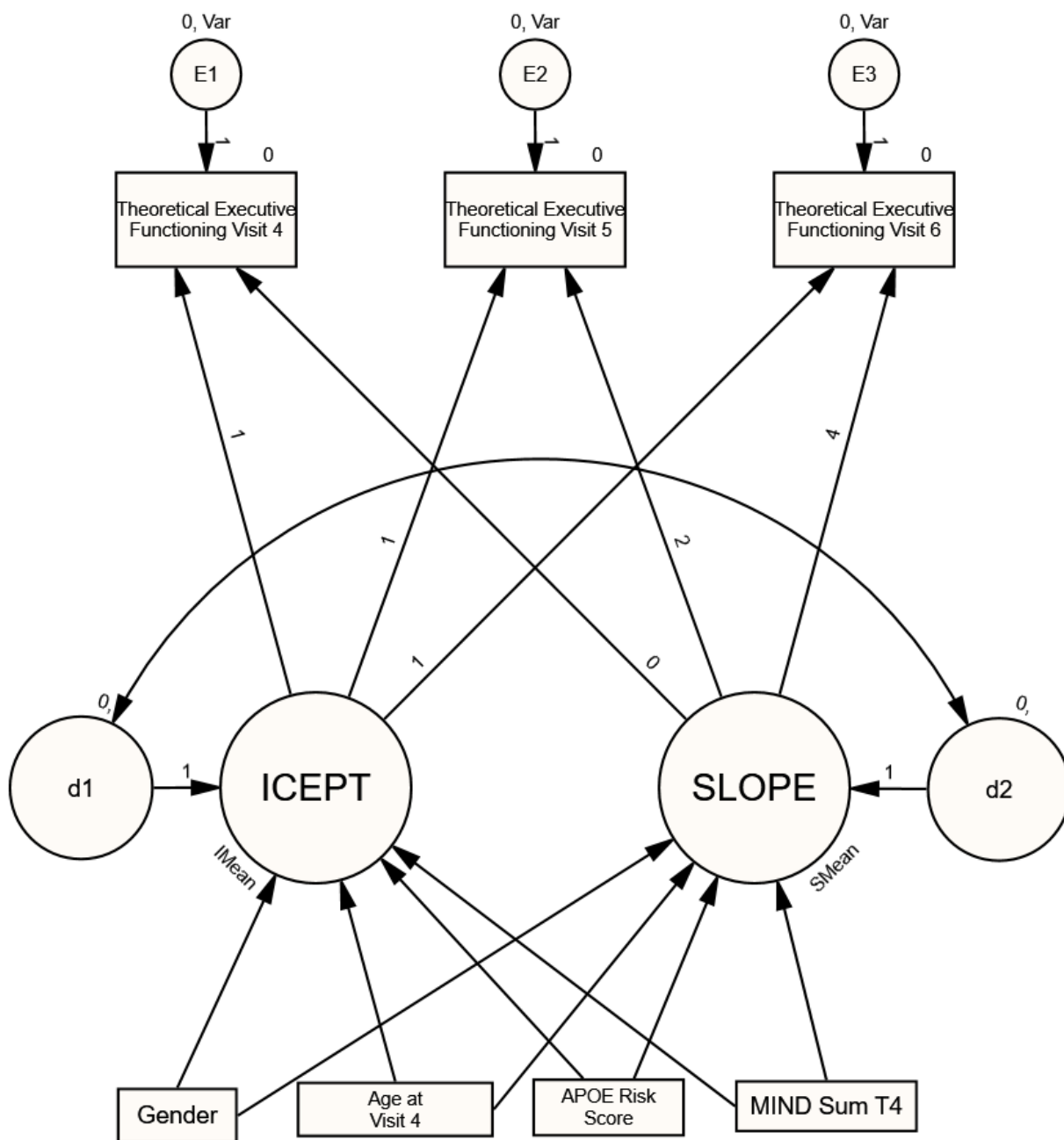
Figure C2

Theoretical Delayed Memory Initial Structural Model



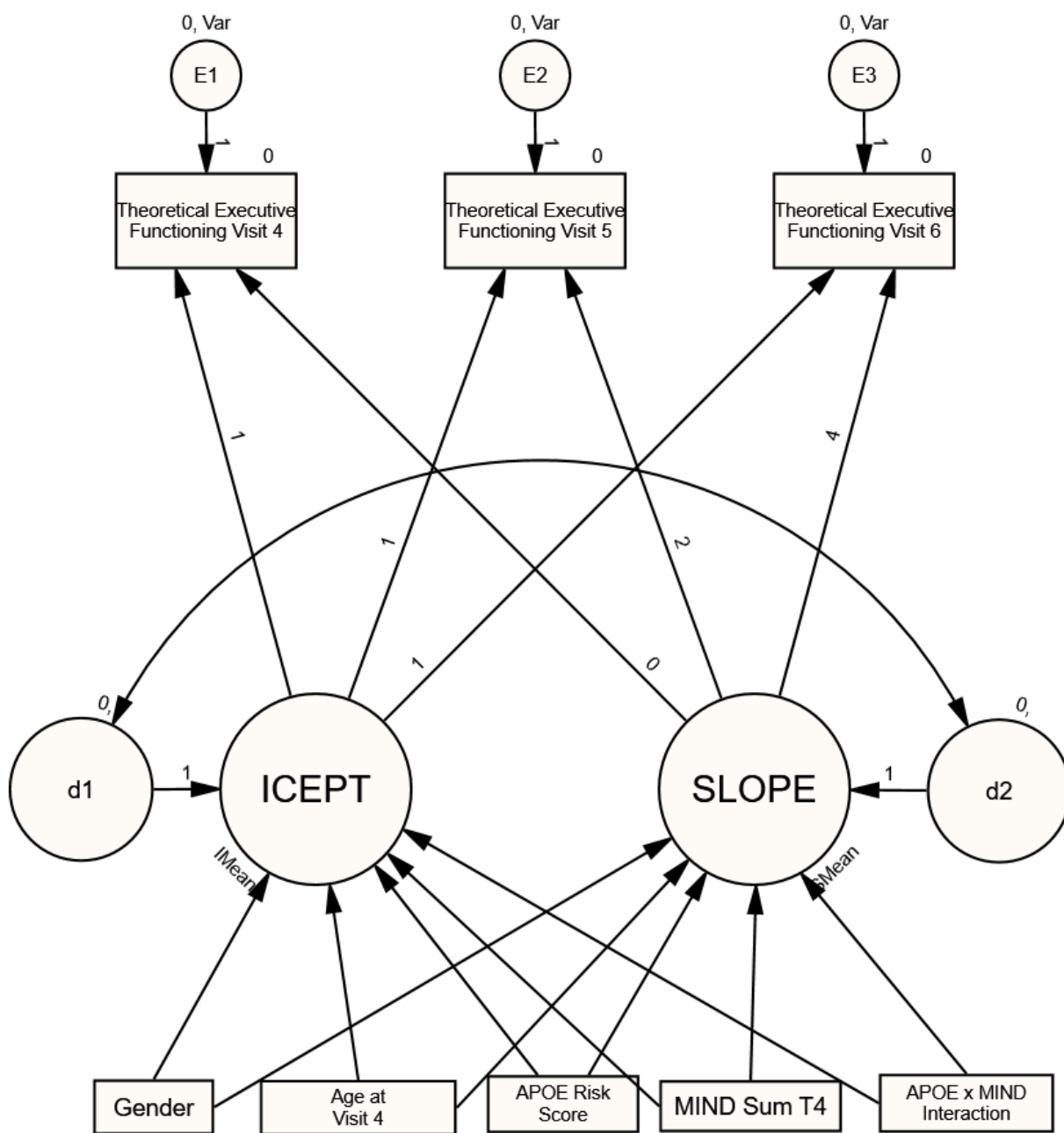
Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

Figure C3

Theoretical Executive Functioning Initial Structural Model

Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

Figure C4

Theoretical Executive Functioning Moderation Structural Model

Note. Parameters from the intercept and slope to the observed variables were fixed. Values 0, 2.0, and 4.0 were assigned to the slope parameters to represent Visits 4, 5, and 6, respectively, therefore, reflecting equal time between visits.

BIOGRAPHY OF THE AUTHOR

Taylor Marie McMillan was born in Scottsdale, Arizona on August 3, 1991 to James and Jessica McMillan. She and her two siblings were raised in Stoughton, Wisconsin. She graduated from Stoughton High School in June 2009. Following high school graduation, she attended the University of Wisconsin-Eau Claire where she received a Bachelor of Arts degree in Psychology with a minor in Kinesiology in December 2013. As an undergraduate, she was awarded the University of Wisconsin-Eau Claire Summer Research Experience Grant. She co-authored one manuscript and one research presentation at a local student symposium, with her research mentor, Jennifer J. Muehlenkamp, Ph.D., and colleagues from Lawrence University (Lori M. Hilt, Ph.D., Peter P. Ehlinger, M.A.).

Taylor began her graduate training at Eastern Illinois University where she received her Master of Arts in Clinical Psychology. She was awarded Distinguished Graduate Student and successfully defended her master's thesis titled *Binge Eating Disorder: Relationship to Physical and Emotional Factors* chaired by Wesley D. Allan, Ph.D. Before pursuing her Doctor of Philosophy in clinical psychology, Taylor worked at the University of Wisconsin Hospital and Clinics in Madison, Wisconsin in the Department of Neurology (2016-2017). She worked as an associate research specialist on a National Institute of Health-funded study, the Epilepsy Connectome Project (principal investigators were Jeffrey Binder, M.D., and Elizabeth Meyerand, Ph.D.). She co-authored one manuscript and presented research (2 posters, 1 moderated presentation) at international conferences.

Taylor continued her graduate training and was admitted to the clinical psychology doctoral program at the University of Maine-Orono in Orono, ME in August 2017 under the mentorship of Fayeza S. Ahmed, Ph.D. As a graduate student, she was a member of the Health

Aging and Lifestyle (HAL) Lab where she assisted with research examining the relationships between health (e.g., physical activity, nutrition, sleep, cardiorespiratory fitness), genetics, affect/mood, and cognition particularly in mid-life. The goal of this research is to examine early risk factors for Alzheimer's disease. She co-authored two manuscripts and 13 research presentations (two oral presentations and 11 poster presentations) at local and international conferences.

Taylor received her Master of Arts in Psychology in August 2018 from the University of Maine and was awarded doctoral candidacy. She completed a second-year independent research project using data from the Maine Syracuse Longitudinal Study. Taylor continued to maintain her collaborations with Bruce Hermann, Ph.D., and Jana Jones, Ph.D., from the University of Wisconsin Madison. In addition, Taylor was a student member of National Academy of Neuropsychology, ISTAART Alzheimer's Association, International Neuropsychological Society, Maine Psychological Association, and the American Psychological Association. She obtained editorial experience through co-mentored manuscript reviews (three, mentor Fayeza S. Ahmed, Ph.D.) and one independent manuscript review. She was awarded four grants/fellowships throughout her graduate training funding research, teaching, and promoting age-friendly healthcare in Maine communities. Taylor held multiple administrative and service positions including Associate Director of the Psychological Services Center, Chair of the Diversity Committee, Co-developer of the Psychological Services Center COVID-19 Stress Clinic, and panel member of a symposium titled Mental Health in Times of COVID-19. She serviced her local community by volunteering at the Bangor Alzheimer's Association Walk to End Alzheimer's and Kenduskeag Fire and Rescue Volunteer Association. During her graduate

training, she received commendation for outstanding contributions to research and for outstanding service.

Taylor is currently completing her predoctoral internship in Clinical Neuropsychology at the University of Florida, Department of Clinical and Health Psychology. After she receives her doctorate, she will remain at the University of Florida to complete a two-year postdoctoral fellowship in Clinical Neuropsychology. She plans to develop clinical expertise working with neurosurgical populations (e.g., epilepsy, brain tumor) and patients with various neurological populations across the adult age spectrum. She plans to conduct clinical research examining the cognitive sequelae of epilepsy, as well as predicting pre-surgical cognitive risk. Taylor is a candidate for the Doctor of Philosophy degree in Psychology from the University of Maine-Orono in August 2023.