LIFESTYLE FACTORS RELATED TO COGNITIVE AGING

APPROVED BY SUPERVISORY COMMITTEE

Heidi Rossetti, PhD, ABPP (Chair)

Laura Lacritz, PhD, ABPP (Co-Chair)

Linda Hynan, PhD

Melissa Lamar, PhD

Eric Smernoff, PhD

Abbey Valvano, PhD

DEDICATION

To my parents who encouraged me, my husband who supported me, and my supervisors who guided me, thank you.

LIFESTYLE FACTORS RELATED TO COGNITIVE AGING

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EMILY ELAINE SMITH

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LIFESTYLE FACTORS RELATED TO COGNITIVE AGING

EMILY ELAINE SMITH, B.S.

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HEIDI ROSSETTI, Ph.D., ABPP

ABSTRACT

Cognitive changes are a hallmark feature of Alzheimer's disease (AD) and lifestyle behaviors have been associated with a reduced risk of disease onset and slower rate of cognitive decline. Research examining the relationship of lifestyle factors (LFs) to brain health has typically focused on individual factors in isolation (more physical activity (PA) and reduced risk of AD); however, few studies have examined the combined effects of multiple LFs on cognition. The current study aimed to 1) determine which LFs best predict cognition cross-sectionally; 2) derive and compare different approaches to developing a Health Score (HS) to help predict cognition; and 3) discern if a healthy lifestyle was associated with slower rate of cognitive decline.

This study included 467 older adults (M_{age}=83; No Cognitive Impairment=361, Mild Cognitive Impairment (MCI=94), Alzheimer's dementia (AD=12)) enrolled in a longitudinal (M_{years}=3.72) aging study with yearly evaluations, including neuropsychological testing, clinical evaluation, and detailed assessment of lifestyle behaviors: diet, PA, sleep, social activities, stress, depression, alcohol, smoking, body mass index (BMI), and APOE genotyping. Cognitive z-scores were derived for global cognition, verbal memory, processing speed, and working memory. HS based on a Scientific (i.e., data driven), Lifestyle/Health (i.e., only healthy lifestyle behaviors), Risk/Disease (i.e., only unhealthy behaviors), or Comprehensive (i.e., all healthy/unhealthy behaviors) approaches were calculated and categorized (Unfavorable, Minimally Favorable, Moderately Favorable, Favorable) based on quartiles. Rate of cognitive change was also calculated.

Multiple linear regression analyses in the full sample revealed demographic and lifestyle (i.e., social activities, diet) factors consistently predicted cognition cross-sectionally. In the MCI/AD group, diet, PA and BMI were significant predictors with minimal demographic predictors. HS comparisons via Meng's test revealed a Lifestyle/Health approach as the best predictor of cognition compared to the other approaches. In addition, individuals with HSs in the Favorable category had significantly slower rates of cognitive decline than individuals in other categories.

Overall, LFs better predicted cognition than risk factors commonly used in clinical and research settings. Results from this study corroborate prior findings and encourage continued support and resources for lifestyle research and intervention programs to help prevent and slow cognitive decline and AD.

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LIST OF DEFINITIONS

3MS – Modified Mini-Mental State Examination

AAN – American Academy of Neurology

Aβ – Amyloid beta

AD – Alzheimer's disease

ADAS-Cog – Alzheimer's Disease Assessment Scale-Cognitive Subscale

ADL – Activities of Daily Living

ANCOVA – Analysis of covariance

ANOVA – Analysis of variance

APOE – Apolipoprotein E

BBB – Blood brain barrier

BDNF – Brain-derived neurotrophic factor

BMI – Body Mass Index

CERAD – Consortium to Establish a Registry for Alzheimer's Disease

CES-D – Center for Epidemiologic Studies Depression scale

COPD – Chronic obstructive pulmonary disease

CSF – Cerebrospinal fluid

DASH – Dietary Approach to Stop Hypertension

FDDNP – 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl-ethylidene)malononitrile

HPA – Hypothalamic pituitary adrenal

HVLT – Hopkins Verbal Learning Test

IADL – Instrumental activities of daily living

MAP – Memory and Aging Project

MCI – Mild Cognitive Impairment

MCT – Medium-chain-triglyceride

MIND – Mediterranean-DASH Intervention for Neurological Delay

MMSE – Mini Mental State Examination

MoCA – Montreal Cognitive Assessment

MRI – Magnetic resonance imaging

NCI – No Cognitive Impairment

NIA – National Institute on Aging

PET – Positron emission tomography

PiB – Pittsburgh Compound-B

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

SES – Socioeconomic status

TL – Telomere length

CHAPTER ONE: Introduction

BACKGROUND

Approximately one in ten American adults over the age of 65 are living with Alzheimer's disease (AD; Alzheimer's Association, 2019). This equates to about 5.8 million current cases and between 500,000 and 900,000 new cases each year (Alzheimer's Association, 2019). AD is the sixth leading cause of death in the United States (Alzheimer's Association, 2019) and with over 400 failed trials, including almost 100 failing during Phase III (equating to a 99.6% failure rate; Cummings, Morstorf, & Zhong, 2014; Mehta, Jackson, Paul, Shi, & Sabbagh, 2017), there is currently no effective treatment. Monotherapy pharmaceutical intervention has been the norm, but a recent literature review conveys the need to consider combination therapies that target multiple pathways of the heterogeneous disease (Cummings, Tong, & Ballard, 2019).

The monotherapy medications (e.g., Aricept, Exelon, Namenda, and Razadyne) prescribed for Mild Cognitive Impairment (MCI) and AD are advertised to slow disease progression, but in 2018, the American Academy of Neurology (AAN) recommended physicians explain the lack of evidence these drugs had for slowing cognitive decline before offering a prescription. Instead of prescribing cholinesterase inhibitors, the AAN advocated for treating behavioral and neuropsychiatric symptoms (Petersen et al., 2018).

Since the pharmaceutical industry has failed to discover a cure for the disease, treatment efforts have shifted to multifactorial interventions targeting risk factors to prevent or delay cognitive decline. Increased risk of developing AD has been attributed to genetic (e.g., apolipoprotein E

allele ε4; APOE ε4), medical (e.g., diabetes, obesity, hypertension, hypercholesterolemia, cerebrovascular disease, sleep disordered breathing, head injury), psychological (e.g., depression, stress), demographic (e.g., older age, low education), and lifestyle (e.g., poor diet, smoking, alcohol abuse, lower social engagement, insufficient physical activity) factors (Cooper, Sommerlad, Lyketsos, & Livingston, 2015; Galvin, 2017; Hersi et al., 2017; Larsson et al., 2017; Pistollato et al., 2016; Rakesh, Szabo, Alexopoulos, & Zannas, 2017). Interestingly, up to 50% of dementia cases and 33% AD cases may be attributed to modifiable risk factors and thus potentially preventable (Ashby-Mitchell, Burns, Shaw, & Anstey, 2017; Baumgart et al., 2015; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Healthy lifestyle behaviors such as nutritious diet, regular physical activity, restful sleep, positive social interactions, and intentional stress reduction have been shown to delay dementia onset. Postponing dementia onset by 12 months would result in over 9 million fewer annual AD cases (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Thus, effective prevention strategies are a public health necessity of increasing interest (Rakesh et al., 2017), and there is a need for high-quality studies that examine the relationship between a combination of lifestyle factors and cognitive outcomes.

Exploring the relationship of lifestyle factors and brain health has taken many forms. Several studies have examined correlations between healthy lifestyle factors and dementia course, specifically Alzheimer's disease. Other studies report hazard or risk ratios of developing a neurodegenerative disorder while others report a specific change in cognition as measured by individual neuropsychological tests, specific cognitive domains, or a global cognition composite score. These studies have been performed cross-sectionally and longitudinally. Additionally, many systematic review papers, some with meta-analysis, have also been published in this area.

The following review will incorporate findings from studies using all of these various methodologies.

CHAPTER TWO: Review of the Literature

RATIONALE FOR LIFESTYLE FACTORS

Nonpharmacological interventions are important to delay and possibly prevent Alzheimer's disease onset because a cure has yet to be discovered and the growing disease incidence rate poses a tremendous global financial and caregiving burden. However, nonpharmacological interventions are less financially lucrative compared to pharmacological treatments and thus given limited attention from the health care community, until recently. Interestingly, a significant percentage of AD cases have been attributed to modifiable causes, which are directly related to lifestyle. Unfortunately, changes in lifestyle behaviors are often overlooked or undervalued by treatment providers, but studies show that though initially skeptical, with education and training, treatment providers become supportive of lifestyle interventions for their patients (Mehl-Madrona & Mainguy, 2017). Similarly, patients enjoy these types of interventions, especially when they are done in groups (Mehl-Madrona & Mainguy, 2017).

Many lifestyle factors have been explored as they relate to Alzheimer's disease, but few studies have looked at multiple factors in combination. Traditionally, research in this area has entered the discussion through a disease-model or risk factor approach. Many studies examine variables that makes outcomes worse while omitting variables that contribute to wellness and health. The focus of this project will be on health factors and specifically on the combined effects of diet, physical activity, sleep, social activities, and perceived stress. Most studies focus on one lifestyle factor and an aspect of brain health, but the goal of this project is to examine the combined effect

of multiple lifestyles factors on cognition and cognitive change over time. The below review discusses each lifestyle factor individually and concludes by presenting studies looking at multiple factors together. In each lifestyle section, studies will be presented related to overall health, incidence of dementia, biomarkers of dementia, and cognition. Limitations of the literature are provided at the end of each section.

HEALTHY DIET

Epidemiological and observational studies, as well as randomized controlled trials have shown a link between diet and cognitive dysfunction (Mosconi & McHugh, 2015). Possible mechanisms for nutritional interventions improving cognitive outcomes are insulin resistance, dyslipidemia, oxidative stress (Schelke et al., 2016) and inflammation (Tangney et al., 2014). Popular interest was initially focused on individual nutrients like omegas (Andrieu et al., 2017; Fonteh, 2018), fruits, and vegetables (X. Jiang et al., 2017), specifically leafy greens (Morris et al., 2018), but have since transitioned into overall dietary patterns (Berendsen et al., 2014; van de Rest, Berendsen, Haveman-Nies, & de Groot, 2015). Researchers have explored many different types of diets including the Dietary Approach to Stop Hypertension (DASH) (Tangney et al., 2014), Mediterranean diet (Davis, Bryan, Hodgson, & Murphy, 2015), Mediterranean-DASH Intervention for Neurological Delay (MIND; Morris et al., 2015), and Adkins/ketogenic diets (Brandt et al., 2019; Morrill & Gibas, 2019). Though there are nuances to each diet, each is whole-foods based and limit refined sugar and processed food (**Table 1**).

Types of diets

The Mediterranean Diet

The Mediterranean diet is arguably the most well-known dietary pattern for healthy living. The Mediterranean diet consists of minimally processed, seasonally fresh, and locally grown foods. It emphasizes plant foods (e.g. fruits, vegetables, unrefined bread and pasta, brown rice, beans, nuts, and seeds), and olive oil with low to moderate amounts of dairy and wine. Red meat and eggs are consumed infrequently and desserts typically consist of fresh fruits or are nut-based and made with olive oil (Serra-Majem, Roman, & Estruch, 2006). This eating pattern was modeled after the typical diets of residents in Mediterranean countries (e.g., Greece and southern Italy) during the early 1960s and is associated with high life expectancy and low rates of coronary artery disease, cancer, and a plethora of chronic diseases (Mastorakou, Rabaeus, Salen, Pounis, & de Lorgeril, 2019; Serra-Majem et al., 2006). It has also been shown to promote cognitive health, slow cognitive decline, and reduce the risk of mild cognitive impairment and Alzheimer's disease (Scarmeas, Stern, et al., 2009; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006; Tangney et al., 2011). Despite extensive literature supporting the cognitive benefits of the Mediterranean diet, some studies have found contrasting results. Studies have reported adherence to the Mediterranean diet did not reduce risk of dementia (Feart et al., 2009), slow cognitive decline (Samieri, Okereke, E, & Grodstein, 2013) or protect against cognitive impairment (Cherbuin & Anstey, 2012), though the studies may have been underpowered (Cherbuin & Anstey, 2012; Feart et al., 2009), and some authors question the quality of the diet data (Samieri et al., 2013). Studies examining the benefit of the Mediterranean diet in mild cognitive impairment are also inconsistent (Lourida et al., 2013). To reconcile this discrepancy, some studies cite the benefit of the holistic "Mediterranean lifestyle" which includes social patterns

and physical activities, in addition to the dietary pattern, as important contributing factors that impact the slowing of cognitive decline (Yannakoulia, Kontogianni, & Scarmeas, 2015), though further investigation is needed to fully understand this concept.

The DASH Diet

The DASH diet was originally established as a Dietary Approach to Stop Hypertension; however, it has been applied to several maladies including cognitive problems and neurodegenerative diseases (Tangney et al., 2014) and used as a dietary component in multifaceted lifestyle interventions (Blumenthal et al., 2019; Blumenthal et al., 2017). The DASH diet is low in saturated fat, cholesterol, and total fat and emphasizes fruits, vegetables, and fat-free or low-fat milk and milk products. The DASH eating plan also includes whole grain products, fish, poultry, and nuts but is reduced in lean red meat, sweets, added sugars, and sugar-containing beverages. It is rich in potassium, magnesium, and calcium, as well as protein and fiber, but low in sodium (Appel et al., 2006; Services, 2006). A food frequency questionnaire and a DASH diet adherence score are used in research. Higher adherence to the DASH diet has been shown to slow cognitive decline over time in non-demented older adults (Tangney et al., 2014). Specifically, for every one unit higher in DASH score, the rate of decline was 0.007 standardized units in community dwelling cognitively normal older adults who were followed for about four years (Tangney et al., 2014).

The MIND Diet

The Mediterranean diet and DASH diet gave way to the MIND diet (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay), which has gained popularity for promoting brain health. The MIND diet was tailored to include specific foods found to be helpful for cognition

and excluded foods that were not beneficial (Morris et al., 2015). The MIND diet score was established from a food frequency questionnaire where participants got points for ten brain healthy foods groups (i.e., green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil and wine) and five unhealthy food groups (i.e., red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Using a proportions chart, a MIND diet adherence score was derived by summing across all 15 food groups (Morris et al., 2015). In a sample of cognitively normal and MCI older adults, participants in the highest tertile of MIND diet adherence scores had a substantially slower rate of global cognitive decline, as measured by an annual cognitive z-score consisting of nineteen neuropsychological tasks, than participants in the lowest tertile of adherence scores (Morris et al., 2015). The difference in rates was the equivalent of being 7.5 years younger in age. Also, higher diet adherence scores were associated with slower decline in episodic memory, semantic memory and perceptual speed (Morris et al., 2015).

Ketogenic or Modified Atkins Diet

Another diet often discussed in the context of health is the Ketogenic or Modified Atkins diet. Traditionally known for use in intractable epilepsy (Peterman, 1925), a ketogenic diet is high in fat and low in protein and carbohydrate in order to induce ketosis, a state in which the body metabolizes fat instead of glucose and produces ketone bodies (i.e., acetoacetic acid and betahydroxybutyric acid). When carbohydrates are eliminated and available glucose is low, the body changes to burn these ketone bodies instead of sugar. The Ketogenic diet is notorious for being strict and difficult to follow; thus, a modified Ketogenic or modified Atkins diet, which liberalizes the ratio of fats to carbohydrates, has been trialed and found to successfully reduce

seizure frequency in epilepsy (Cervenka, Patton, Eloyan, Henry, & Kossoff, 2016; Kossoff, Rowley, Sinha, & Vining, 2008). The Ketogenic diet has more recently been applied to Alzheimer's disease because of the mechanistic similarities. It is well known that Alzheimer's disease patients have impaired glucose uptake in their brains, and studies have shown that decreased glucose uptake is strongly correlated with severity of cognitive impairment (Mosconi et al., 2009). PET imaging studies suggest that brain metabolism of ketone bodies is unimpaired in AD patients even when glucose metabolism is extremely low (Castellano et al., 2015; Croteau et al., 2018). The few trials that have implemented Ketogenic diets in patients with MCI or AD have small sample sizes and soft methods. A case study report of a 71-year-old female with MCI, metabolic syndrome, APOE ε4 and a family history of AD showed improved Montreal Cognitive Assessment (MoCA) performance (21/30 to 28/30) after a 10-week modified Ketogenic nutrition intervention (Morrill & Gibas, 2019). A feasibility study with nine MCI/AD participants in the intervention arm found that if ketosis can be induced, there may be at least temporary improvement on a memory composite score (sum score of the delayed recall trials for the Hopkins Verbal Learning Test – Revised and the Brief Visuospatial Memory Test – Revised), but the authors noted extreme difficulty with adherence and non-significant differences in cognitive scores (Brandt et al., 2019).

Other studies looking at exogenous ketone have shown promising results (for review see (Wlodarek, 2019)). Exogenous ketones are given as a supplement without changing the diet. Individuals (n=20) with MCI or AD given medium-chain-triglyceride (MCT) treatment showed improved cognitive performance compared to the placebo group on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) for APOE ε4− participants, but not for ε4+

subjects (Reger et al., 2004). Similar results have been found in other studies (Henderson et al., 2009; Ota et al., 2019), with higher ketone values associated with greater improvement in cognitive tests with MCT treatment relative to the placebo across all participants (Reger et al., 2004). More research is needed to better understand the long-term benefits of exogenous ketones.

Healthy diets and incidence of cognitive disorders

Due to the limited cognitive data available in some research paradigms, many studies examine diet as it relates to the incidence risk of dementia or other cognitive disorders (e.g., MCI). Various diets have been explored and differing results have emerged depending on the population and specifics of the diet. In a systematic review with meta-analysis, the Mediterranean diet adherence score was inversely associated with developing cognitive disorders, and in a dose-response analysis the researchers found a linear trend, suggesting the higher adherence to a Mediterranean diet, the lower the risk of cognitive disorder (Wu & Sun, 2017). In contrast, in a population-based cohort study with over 8000 participants, midlife adherence to the Alternate Healthy Eating Index, a diet reflecting the national dietary guidelines, was not significantly associated with subsequent risk for dementia (Akbaraly et al., 2019). The authors questioned the methodological integrity of diet adherence assessment and the actual health of the national dietary guidelines. Despite these conflicting results using different diets, MIND diet adherence has shown promising results as it relates to neurodegeneration (Morris et al., 2015), and possibly better than the Mediterranean diet. Hoskinga and colleagues reported that MIND diet adherence, but not the Mediterranean diet, reduces the odds of cognitive decline (Hosking, Eramudugolla, Cherbuin, & Anstey, 2019).

Diet and biomarkers

Biomarkers are often called upon to help detect disease presence and track progression, and there is an entire emerging field called nutritional cognitive neuroscience that uses neuroimaging to understand the impact of nutrition on brain function (Zamroziewicz & Barbey, 2016). AD biomarkers have been associated with adherence to the Mediterranean diet. In cognitively normal older adults, stronger adherence to the Mediterranean diet was associated with less AD biomarkers (i.e., less glucose hypometabolism via FDG-PET and less amyloid deposition via Pib-PET) compared to those with poor adherence (Berti et al., 2018). This suggests greater accumulation of AD pathology in individuals with lower adherence to the Mediterranean diet compared to individuals with higher adherence. The study also suggested that higher Mediterranean diet adherence was estimated to provide 1.5 to 3.5 years of protection against brain aging (Berti et al., 2018). Interestingly, no effects were seen on volumetric MRI (Berti et al., 2018).

Cognition

Several studies report relationships between cognition and dietary patterns. In a study of 23 adults with MCI randomized to a six-week low carbohydrate or high carbohydrate diet, participants with low carbohydrate diet had improved verbal memory performance on the Verbal Paired Associate Learning Test compared to the high carbohydrate diet (Krikorian et al., 2012). In a group of older adults at high vascular risk, a Mediterranean diet supplemented with extra virgin olive oil and mixed nuts resulted in better MMSE and clock drawing scores compared to a low-fat diet control group over a 6.5 year longitudinal study; however, the cohort was not

cognitively assessed at baseline so results should be interpreted with caution (Martinez-Lapiscina et al., 2013). In studies examining dietary patterns, it is common for researchers to create a composite score combining several tests from a single domain or from various cognitive domains. When using a memory composite score, consisting of delayed recall from the Brief Visuospatial Memory Test –Revised (BVMT-R) and Hopkins Verbal Learning Test-Revised, adults with MCI or early AD participating in a Ketogenic diet intervention experienced improvements in their memory composite score after 12 weeks (Brandt et al., 2019). Similarly, in a group of healthy older adults, those with higher adherence to a healthy diet showed statistically significant improvements in global cognition and episodic memory after one year, compared to those with lower adherence (Marseglia et al., 2018). In a cross-sectional study, better diet was related to better memory, visual–spatial abilities, and language function in non-demented older adults (Anastasiou et al., 2018). In a group of community dwelling adults (ages 50+), higher adherence scores to the Mediterranean and MIND diets were independently associated with significantly better cognitive function in a dose response manner (McEvoy, Guyer, Langa, & Yaffe, 2017). These results provide strong evidence that healthy diets support healthy cognitive functioning.

Though there are a handful of individual studies questioning the utility of the Mediterranean diet for slowing cognitive change, the majority of articles, including review papers and meta-analyses, support the use of the Mediterranean diet with some differing effects in various cognitive domains. The strongest metanalytic evidence suggests a beneficial effect of the Mediterranean diet on healthy older adults' global cognition (Loughrey, Lavecchia, Brennan, Lawlor, & Kelly, 2017). Meta-analysis of healthy older adult *cohort studies* revealed a

significant association between Mediterranean diet and episodic memory and global cognition but not working memory or semantic memory (Loughrey et al., 2017), whereas meta-analysis of *randomized control trials* revealed that those on the Mediterranean diet demonstrated improved delayed recall, working memory, and global cognition, but not episodic memory, immediate recall, paired associates, attention, processing speed, or verbal fluency compared to those on their habitual diet (Loughrey et al., 2017). Another review paper revealed that higher adherence to a Mediterranean diet was associated with slower rates of cognitive decline, reduced conversion to Alzheimer's disease, and improvements in cognitive function, in adults (ages 19-75+). Specific cognitive domains found to benefit from improved Mediterranean diet score were memory (delayed recognition, long-term, and working memory), executive function, and visual constructs (Hardman, Kennedy, Macpherson, Scholey, & Pipingas, 2016). Overall, studies examining cognition and diet suggest that a healthy diet positively impacts global cognition and aspects of memory.

Limitations with diet literature

Despite relatively consistent findings that various healthy diets are beneficial for brain health, especially when compared to the typical American diet, there are many limitations in the existing body of literature. First, some studies do not see an effect of specific diets on cognitive outcomes (Andrieu et al., 2017; Berendsen et al., 2017), though some of these diets lack nutritional rigor (e.g., do not have enough vitamins, minerals, fiber, etc.) or are underpowered to see an effect (Cherbuin & Anstey, 2012; Feart et al., 2009). Adherence is a significant challenge as diets are difficult for anyone to follow, but especially challenging for a person who may be cognitively compromised (Brandt et al., 2019). Further complicating the picture are the challenges associated

with measuring diet/nutritional data (Morris, 2016), especially when self-report is the primary means of measurement. One self-report study found that older adults typically do not follow a DASH or Mediterranean diet plan even though adherence scores are derived (Blumenthal et al., 2017). Socioeconomic status is not often accounted for in these types of studies and there is a lack of research looking at diet scores and nutritional interventions in lower SES populations (Wright, Gerassimakis, Bygrave, & Waldstein, 2017). Lastly, the cognitive outcomes used in studies are often not well established neuropsychological assessments or a non-cognitive assessment is used as a proxy for cognition (i.e., using heart rate as a cognitive correlate; Mantantzis, Maylor, & Schlaghecken, 2018). Much research is needed to better understand the relationship between healthy diets and cognition, though the current literature is certainly promising.

PHYSICAL ACTIVITY AND EXERCISE

Physical activity/exercise is a heavily researched health behavior because it is linked to preventing, decreasing risk, and ameliorating effects of many chronic illnesses, including brain-related diseases. The Department of Health and Human Services (DHHS) recommends 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity (Services, 2018). Furthermore, they propose that additional benefits are gained when engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week (Services, 2018). There are supplementary guidelines for older adults that recommend balance training as well as aerobic and muscle-strengthening activities.

Physical activity and/or exercise has a reputation for being a panacea for chronic illness including cognitive decline. Exercise has been linked to improved symptoms and reduced pain in fibromyalgia (Jones, Adams, Winters-Stone, & Burckhardt, 2006), less fatigue in multiple sclerosis (Motl & Sandroff, 2015), reduced anxiety, depression and other mood disorders (Byrne & Byrne, 1993), better appetite control in obese individuals (Martins, Morgan, & Truby, 2008), improved motor symptoms in Parkinson's disease (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008), better exercise tolerance in COPD (Chavannes, Vollenberg, van Schayck, & Wouters, 2002), and higher quality of life in cancer (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006), among many other chronic maladies. Meta-analysis and systematic review suggest that exercise interventions positively influence cognitive function in patients with chronic diseases, independent of the disease, type of exercise, exercise frequency, and the intensity of the exercise intervention (Cai, Li, Hua, Liu, & Chen, 2017).

A connection between exercise and reduced risk of cognitive decline has been well established in the literature for almost four decades. Early literature that emerged in the 1980s and 1990s made the connection between physical activity/exercise and reduced risk of cognitive decline (Chodzko-Zajko, 1991; Clarkson-Smith & Hartley, 1989; Dustman et al., 1984; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Rogers, Meyer, & Mortel, 1990; Stacey, Kozma, & Stones, 1985). More recent studies have looked at different cognitive domains and specific types of exercise intervention. Studies performed prior to 2001 were incorporated into a meta-analysis which revealed exercise had the greatest effect on executive function, but also had an effect on spatial and speed tasks (Colcombe & Kramer, 2003). This meta-analysis examined

longitudinal intervention studies and found that incorporating both strength and aerobic exercise resulted in a larger cognitive effect size compared to aerobic exercise alone (Colcombe & Kramer, 2003). More recent meta-analyses corroborate these findings, suggesting exercise is robustly (supported by 26 of the 27 articles from one meta-analysis and 13 of 14 articles in another meta-analysis) beneficial for cognition in older individuals (ages 60+) with or without mild cognitive impairment or cognitive disease (Carvalho, Rea, Parimon, & Cusack, 2014; Hernandez et al., 2015) and may be protective against cognitive decline and dementia later in life (Macpherson, Teo, Schneider, & Smith, 2017). However, findings are less clear in demented samples. For example, though Alzheimer's disease patients without cardiovascular problems may benefit from exercise, one study cautions that exercise may, in individuals with high cardiovascular burden, have deleterious effects on cognition (e.g., compromised vasculature may result in the body rerouting blood to the muscles and organs to support the physical activity at the expense of sending blood to the brain) (Eggermont, Swaab, Luiten, & Scherder, 2006). With almost half (47%) of Americans being at risk for cardiovascular disease (Fryar, Chen, & Li, 2012), this study underscores the importance of tailoring recommendations for each patient in the context of their other health conditions. In these cases, physical activity and exercise should not be avoided, but instead tailored to the individuals' needs by starting with a conservative amount at low intensity and increasing the duration and intensity as the individual is able to tolerate it.

Exercise recommendations: type, intensity, and frequency

Type: A popular question is often related to type of exercise for maximal cognitive benefit. The cognitive benefits of aerobic exercise have been widely studied, but more recently, other types of exercise, like resistance training, have been explored. A study examining the cognitive and

imaging effects of twice-weekly resistance training found functional changes on fMRI in two regions of cortex (i.e., the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral orbital frontal cortex) previously associated with response inhibition processes and improved task performance in non-demented (MMSE ≥ 24) older women (ages 65-75; Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012). In another cohort of women (ages 70-80) with subjective memory complaints at risk for probable MCI, six months of twice-weekly resistance training improved selective attention/conflict resolution, associative memory, and regional patterns of functional brain plasticity, compared with twice-weekly balance and tone exercises (Nagamatsu, Handy, Hsu, Voss, & Liu-Ambrose, 2012). These studies suggest both healthy and at-risk individuals may benefit from resistance training. A meta-analysis that compared aerobic training, stretching, and weight lifting in a group of healthy older adults (65+) concluded that a multicomponent exercise program is superior to one type alone (Saez de Asteasu, Martinez-Velilla, Zambom-Ferraresi, Casas-Herrero, & Izquierdo, 2017). This was corroborated by another study that provided recommendations for both aerobic and resistance exercise (Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018).

Intensity: Intensity of exercise has been explored as it relates to MCI and results suggest light- but not vigorous-intensity physical activity significantly reduced the risk of incident MCI (Krell-Roesch et al., 2016). The authors included the caveat that not many older adults exercised vigorously which may account for a non-significant relationship with vigorous activity (Krell-Roesch et al., 2016). In fact, another work with non-demented older adults showed that both higher and low-to-moderate levels of physical activity were associated with greater risk reduction (38%, and 35%, respectively) of cognitive decline compared to sedentary adults (Sofi et al., 2011). This was a review based on hazard ratios derived from longitudinal cognitive

testing. Results suggest there is increased protection with greater intensity of physical activity (Sofi et al., 2011). A Swedish study found a similar dose-response relationship in that older females with “high” fitness, defined on an annual cardiovascular fitness test, had delayed age at dementia onset by 9.5 years and time to dementia onset by 5 years compared to “medium” fitness group (Horder et al., 2018).

Frequency: In terms of frequency, a dose response relationship has been well documented in that more frequent exercise or physical activity yields more favorable results. According to the DHHS, the publishing organization of the national exercise guidelines, additional benefits are gained by engaging in physical activity beyond the weekly recommended amount (Services, 2018). One study using tertiles to measure high, medium, and low exercise frequency found a gradual reduction in risk of AD for the highest tertile compared to the lowest (Scarmeas, Luchsinger, et al., 2009). This effect has also been shown in individuals who are more physically active, not exclusively those who explicitly exercise. An inverse linear dose-response relationship has been shown between leisure time physical activity (e.g., sports exercises, recreational activities, or activities excluding occupational and commuting activities) and incidence of all-cause dementia and Alzheimer’s disease. Specifically, an increase in leisure time physical activity by 10 metabolic equivalent of task hours per week (MET-h/week or 500 kcal/week) was associated with a 13% decreased risk of AD and a 10% decreased risk of all cause dementia (Xu et al., 2017).

Together, these results suggest that any type of exercise at a regular frequency is beneficial for cognition. Multicomponent exercise protocols at higher intensities are related to better cognitive outcomes, but single exercise types at light/moderate intensity also show relationships with

improved cognitive outcomes. Evidence suggests a dose response relationship in that the more frequent exercise the greater the risk reduction. Lastly, the impact of exercise on cognition in the context of cardiovascular risk may lead to decreased cognition.

Physical activity and incidence of cognitive disorders

Many studies have explored the relationship between exercise and incidence of MCI and AD. In a population-based, prospective cohort study, engaging in physical activity in mid- and late life was associated with lower risk of incident MCI (Krell-Roesch et al., 2016). Participants who did have MCI and engaged in moderate intensity physical activity during midlife were found to have significantly decreased risk of dementia (Krell-Roesch et al., 2018), particularly when the activity was of moderate intensity (compared to light or vigorous; Krell-Roesch et al., 2018). In a community sample of older adults measuring physical activity with actigraphy, higher level of total physical activity reduced AD risk over 4 years (Buchman et al., 2012).

Physical activity and biomarkers

There have been several types of biomarkers examined in relation to physical activity/exercise and Alzheimer's disease including genetics (e.g., APOE ε4), cerebral spinal fluid (e.g., Aβ, tau), and brain volumetric measurements in MRI (e.g., hippocampal atrophy), to name a few, with rodent models used to explore and propose mechanisms of why exercise is good for the brain. Researchers found that voluntary wheel running accelerated glymphatic clearance but not blood brain barrier (BBB) permeation, improved astrocytic water channel aquaporin 4 expression and polarization, attenuated the accumulation of amyloid plaques and neuroinflammation, and ultimately protected mice against synaptic dysfunction and a decline in spatial cognition which

suggests possible mechanisms for exercise-induced neuroprotection in the aging brain (He et al., 2017).

In human studies, when looking at genetic markers, exercise has been known to reduce reactive oxygen species, increase cerebral blood flow, and increase brain-derived neurotrophic factor (BDNF; Radak et al., 2010). BDNF is a mediator of neurogenesis and can reverse synapse deterioration and decrease APOE ε4 expression (Radak et al., 2010). APOE ε4 is a well-known genetic risk factor for Alzheimer's disease; however, cognitively normal older adults (ages 50-65) with a family history of AD underwent an eight-month exercise intervention and testing post-intervention revealed improvements in memory performance in both APOE ε4+ and APOE ε4- groups (Etnier et al., 2018) again suggesting that even with genetic vulnerability, lifestyle factors can improve cognition. Similar findings were revealed in a study where a polygenic risk score was derived from cerebrospinal fluid and found that in a late-middle-aged cohort, cardiorespiratory fitness attenuated the adverse influence of genetic vulnerability on CSF biomarkers, which supported the notion that increased cardiorespiratory fitness may be beneficial to those at increased genetic risk for AD (Schultz et al., 2017). Furthermore, in a cognitively normal population, those who met American Heart Association exercise guidelines (i.e., relatively active individuals) had lower Pittsburgh Compound-B (PiB) uptake during PET scan suggesting less amyloid in the brain (Liang et al., 2010).

Imaging studies have also been used to explore the relationship with exercise and biomarkers of AD. MRI scans of older adults who engaged in aerobic exercise intervention for one year showed increased size of the anterior hippocampus (about 2%, which is equivalent to 1-2 years

of normal aging volume loss) and improved spatial memory (Erickson et al., 2011), providing support that exercise may be a way to preserve memory functioning; though in this study, only spatial memory was improved. Increased hippocampal volume was also associated with increased levels of BDNF (Erickson et al., 2011).

The benefit of exercise is further highlighted in a study of younger patients (M_{age}; SD=38; 10) with dominantly inherited Alzheimer's disease (n=372), which is a genetic form of AD caused by an autosomal dominant mutation on the PSEN1, PSEN2, or APP gene. Results from the study found that mutation carriers with high physical activity scores performed substantially better on Mini Mental State Examination (MMSE) at expected symptom onset and fulfilled the diagnosis of very mild dementia 15.1 years later compared with low exercisers (Muller et al., 2018). These results suggest the robust benefit of exercise, even in genetically vulnerable groups.

Cognition

Few exercise studies incorporate detailed neuropsychological assessments, but those that do collect cognitive data provide helpful information in determining which cognitive domains are most influenced by exercise or physical activity. Global cognition has been shown both cross-sectionally as well as longitudinally to be associated with exercise. In a cohort of 521 older adults without dementia, physical activity measured via an actigraph device was associated with a global cognition composite score even when adjusting for age, sex and education (Buchman, Wilson, & Bennett, 2008). In the same cohort, but longitudinally, the same objective measure of physical activity was associated with rate of global cognitive decline over about 4 years (Buchman et al., 2012).

Other studies look at specific cognitive domains as influenced or as associated with exercise. In an observational study of non-demented older adults, participants who were more physically active had better memory, were cognitively faster and had better executive skills (Anastasiou et al., 2018). In a different study looking at multiple cognitive domains in cognitively healthy older adults, processing speed, as measured by the RBANS, had the most robust link with exercise, as measured by pedometer data (Calamia et al., 2018). Memory findings have been mixed. One study found spatial memory improved after aerobic exercise intervention in older adults (Erickson et al., 2011), while another study found that higher levels of physical activity were associated with better verbal memory (as measured by the HVLT) but not visual memory (complex figure; Blumenthal et al., 2017). Regarding executive functioning, resistance exercise improved executive function, at least transiently, in healthy older adults compared to a control group who watched a exercise-related video (Naderi et al., 2019). They found that exercise at moderate intensity versus low intensity afforded greater executive function gains (Naderi et al., 2019).

Activities of daily living have also been examined as they relate to exercise. Meta-analysis of AD patients over the age of 65 showed improved ADL functioning (or slowed ADL decline) in the exercise groups compared to the control groups (Rao, Chou, Bursley, Smulofsky, & Jezequel, 2014). Similarly, nursing home patients with AD who did or did not engage in a two-week exercise intervention had significant ADL decline, but the decline was significantly lower in the exercise group after twelve months of participating (Rolland et al., 2007). Interestingly, there was no difference at six months, suggesting some kind of dose-response effect (Rolland et al.,

2007). The authors calculated that the patients in the exercise program declined approximately one-third as much as the routine medical care patients (Rolland et al., 2007).

Intriguingly, there seem to be sex differences associated with exercise and cognition. In a group of amnestic MCI patients, women's cognition was improved with exercise, especially executive function tasks like selective attention, search efficiency, processing speed, and cognitive flexibility, but men did not reap the same benefits (Baker et al., 2010). Similar findings were seen in another study where cognitively normal (MMSE $\geq$ 26) women and men underwent the same strength training intervention, but only women had improvements in executive functioning compared to men and compared to controls (Naderi et al., 2019). Overall, it appears that women's cognition is more likely than men's cognition to be impacted with exercise, for reasons that continue to be explored.

Limitations in the physical activity/exercise literature

Similar to the limitations in the diet literature, exercise and physical activity are subject to self-report bias and error in observational studies that may be further pronounced in a memory impaired sample. There is no gold standard for how exercise and physical activity are measured; there is no a designated device or standardized questionnaire. Nor is there standardization of exercise intensity; light, moderate, and vigorous exercise are defined for each study. Another challenge is the generalizability of the outcomes. Some studies that have specific, time-limited exercise protocols are not realistic interventions outside of a research setting, so the results are interesting, but perhaps not clinically relevant. Lastly, many studies do not capture cognitive data on well-established neuropsychological measures, but when they do, especially in shorter

interventions, they are vulnerable to practice effects. Conversely, neuropsychological measures are often critiqued for not being sensitive to subtle changes and thus may not accurately capture cognitive change after an exercise intervention. There is certainly a need for longitudinal, well-controlled, and ecologically realistic studies that can be used to inform clinical recommendations for patient populations and the general public.

SLEEP

Sleep is an essential biological human function and important for health and wellness. In an 85-year life span, an individual may sleep nearly 250,000 hours, which is equivalent to over 10,000 full days (Scullin & Bliwise, 2015). Sleep serves many functions, including tissue restoration (Adam & Oswald, 1977) and brain metabolite clearance (Xie et al., 2013). In an animal study, sleep enhanced the removal of potentially neurotoxic waste products that accumulated in the awake central nervous system (Xie et al., 2013), which highlights the important clean-up work that goes on during sleep. Sleep recommendations put forward by the Sleep Research Society and the American Academy of Sleep Medicine suggest healthy adults should regularly obtain seven or more hours of sleep per night to promote optimal health and functioning, and there are potentially adverse health outcomes when consistently sleeping more than nine hours per night (Watson et al., 2015). Fewer than seven hours is associated with greater likelihoods of obesity, high blood pressure, diabetes, coronary heart disease, stroke, mental distress, and death (Liu, 2016). In a large nation-wide survey looking at the prevalence of guidelines adherence, 65.2% of adult respondents reported sleeping seven or more hours per night (Liu, 2016), with the highest adherence (73.7%) among the older adult age group (65+) (Liu, 2016).

There are many reasons for insufficient or excessive sleep, and the terminology and definitions in the literature are also varied. Sleep disordered breathing interferes with adequate sleep. Insomnia symptoms include difficulty falling asleep, staying asleep, and poor sleep quality (Spira, Chen-Edinboro, Wu, & Yaffe, 2014). Some studies rely on self-report of sleep duration and others utilize objective measures. Polysomnography is the gold standard assessment tool for sleep, but actigraphy, a method of estimating sleep/wake patterns by recording movement over multiple days using a device typically worn on the wrist, is also used (Spira et al., 2014).

Sleep has an important role in cognitive functioning, especially in older adults. The relationship between sleep disturbance and aging has been known for decades but the mechanism of action is debated. A commonly accepted pathway is that sleep loss causes inflammation (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006) and inflammation causes cognitive decline (Yaffe et al., 2003) and AD pathology (Rogers et al., 1996). Some believe that approximately 15% of AD cases may be attributed to sleep problems (Bubu et al., 2017). Some researchers posit a bidirectional relationship between disordered sleep and AD (Ju, Lucey, & Holtzman, 2014) such that sleep deprivation causes an accumulation of amyloid beta in the brain, thus disrupting the sleep-wake cycle and increasing the risk of cognitive symptoms of a neurodegenerative disease. Conversely, Aβ plaques in the brain cause sleep-wake disturbances, hence the bidirectional relationship (Ju et al., 2014). This is perhaps why sleep disturbances occur more frequently in older individuals with dementia than in those who are nondemented (Prinz et al., 1982).

Sleep and incidence of cognitive disorders

Although it is unclear whether dementia causes sleep problems or sleep problems cause dementia, inadequate sleep is consistently linked to dementia risk. Independent of demographics and vascular risk factors, sleep inadequacy and increased daytime sleepiness were found to be risk factors for dementia in older adults (65+) (Tsapanou et al., 2015). On the opposite end of the sleep duration spectrum, prolonged sleep (>9 hours) was also associated with an increased risk of incident dementia (Larsson & Wolk, 2018; Westwood et al., 2017). One study created a sleep disturbance index score based on the following items: sleeping problems and fatigue in the past six months, sleep medication use, and recent trouble sleeping or a change in sleep pattern (Sterniczuk, Theou, Rusak, & Rockwood, 2013). This index score was associated with self-reported or proxy-reported dementia or Alzheimer's disease within approximately four years. Specifically, they found that higher scores on the index were associated with 23% greater odds of dementia or Alzheimer's disease after accounting for demographic variables, BMI, and baseline cognitive performance (Sterniczuk et al., 2013). Similar results were found using an objective sleep measure (actigraphy device on wrist) in a sample of community dwelling older adults, with a higher level of sleep fragmentation (i.e., more disrupted sleep) being associated with incident AD and rate of cognitive decline (Lim, Kowgier, Yu, Buchman, & Bennett, 2013). Meta-analytic results further substantiate the relationship between poor sleep and dementia. When compiling the results of 27 observational studies, Bubu and colleagues concluded that individuals with sleep problems had a 1.55 (95% CI: 1.25–1.93), 1.65 (95% CI: 1.45–1.86), and 3.78 (95% CI: 2.27–6.30) times higher risk of AD, cognitive impairment, and preclinical AD (i.e., presence of AD-related biomarkers) than individuals without sleep problems, respectively (Bubu et al., 2017).

Sleep and biomarkers

There have been several types of biomarkers examined in relation to sleep, aging and neurodegenerative disease including volumetric measurements, PET tracer uptake, cerebrospinal fluid, and genetics. In community-dwelling older adults grouped into short (<6 hours), normal (6-9 hours), or long (>9hours) sleep duration, the long duration group was associated cross-sectionally with smaller total cerebral brain volume (Westwood et al., 2017). After only one night of sleep deprivation, healthy controls (ages 22-72) had more Aβ in their brain compared to when they had a rested night of sleep, as measured by F18 uptake on PET scan (Shokri-Kojori et al., 2018). Similarly, using the PiB-PET tracer, reports of shorter sleep duration and poorer sleep quality were associated with greater Aβ burden among community-dwelling older adults (ages 53-91) (Spira et al., 2013).

Cerebrospinal fluid studies report similar findings. In a cross-sectional study of 142 cognitively normal middle-aged and older adults, those with lower levels of CSF Aβ42, an indication of greater brain Aβ burden, had worse sleep as measured by poorer actigraphic sleep efficiency (Ju et al., 2013). Despite a consistent relationship, it is unclear whether Aβ deposition is a cause or a consequence at different points in the Alzheimer's disease course, or whether disturbed sleep and Aβ plaques have a shared cause (Ju et al., 2014). Better sleep, defined as low sleep fragmentation, moderated the association between APOE ε4 and cognitive decline, incident Alzheimer's disease, and postmortem density of neurofibrillary tangles. Less sleep fragmentation was associated with better outcomes, despite presence of APOE ε4. Worse sleep was associated

with a stronger relationship between the ε4 allele and cognitive decline, incident Alzheimer's disease, and postmortem density of neurofibrillary tangles (Lim, Yu, et al., 2013).

Cognition

Sleep has been extensively examined in relation to cognitive functioning, and a full examination of this literature is beyond the scope of this work (for review see Deak & Stickgold, 2010). However, sleep loss has long been recognized to impair attention and executive-control (Scullin & Bliwise, 2015) and interfere with memory consolidation, even in healthy adults (for review see Rasch & Born, 2013). Sufficient sleep has been associated with better visuospatial function (Anastasiou et al., 2018). In older adults, poor sleep quality can be an early sign of cognitive decline (Potvin et al., 2012). Longitudinal studies have found that disrupted sleep, or high sleep fragmentation, was associated with a significant increase in rate of annual cognitive change (Lim, Kowgier, et al., 2013), suggesting that worse sleep is associated with accelerated cognitive decline. Overall, cognition in older adults is vulnerable to the effects too much, too little, or fragmented sleep.

There is some evidence suggesting sleep impacts men and women differently. In older men, an overall measure of self-report sleep quality was linked with cognitive impairment, as measured by the MMSE, when assessed one year later (Potvin et al., 2012). The results also linked short sleep duration (≤ 5 hours) in men but long duration (>9 hours) in women with evidence of amnestic cognitive impairment (Potvin et al., 2012). Global cognitive impairment was linked with reduced sleep efficiency (time asleep divided by time in bed) in men (Potvin et al., 2012), and short sleep duration (≤ 5 hours) in women (Tworoger, Lee, Schernhammer, & Grodstein,

2006). Further supporting these results, another study found that men who were awake for more than an hour and a half after initially going to sleep, compared to men who were awake for less than an hour and a half after initially going to sleep, scored significantly worse on the Modified Mini-Mental State Examination (3MS) and were significantly slower on Trails B (Blackwell et al., 2011). In that same cohort of community dwelling older men, long sleepers (more than eight hours measured objectively via actigraph and subjectively via self-report) scored significantly worse on cognitive measures (Blackwell et al., 2011). Though there were some variations in the results between sleep measured objectively versus subjectively, long sleepers scored worse on the 3MS and took longer to complete Trails B and Digit Vigilance Test. Sleep efficiency has been a problem for women too. Women who regularly had difficulty falling or staying asleep had worse global cognitive scores compared with those who rarely had difficulty sleeping (Tworoger et al., 2006). To appreciate the impact of this effect, the authors noted that the mean differences in cognitive scores was equivalent to 4 to 5 years of cognitive aging.

The relationship between sleep and cognition also varies by education and socioeconomic status. For example, a study of older adults (ages 65+) found that the association between low neighborhood SES, poor sleep quality, and cognitive decline was roughly equivalent to the association between APOE ε4 and cognitive decline (Hunter et al., 2018). Another study found that in a cohort of older adults, prolonged sleep duration was associated with increased risk of incident dementia, but the effect was driven by individuals without a high school degree (Westwood et al., 2017). More studies are needed across various socioeconomic groups to understand the impact of SES on sleep and cognition.

Limitations with sleep literature

Unlike the multiple diet interventions and diet scores, or exercise protocols that incorporate various intensities, frequencies, and durations, sleep is a relatively singular behavior. This reduces some of the variability in comparing studies; however, there are certainly different ways to classify sleep (e.g., long, normal, short, sufficient vs insufficient, disrupted vs uninterrupted), different aspects to consider (e.g., sleep medications, breathing problems, time awake after falling asleep, etc.), and different assessment techniques (e.g., self-report versus objective actigraph). The discrepant language can make comparing studies challenging.

SOCIAL INTERACTION

Social interaction and social connection have been studied as they relate to a multitude of populations and health conditions, including conditions involving cognitive decline. Examining the abundant evidence of social interaction influence on general health behaviors and physical health outcomes may shed light into the mechanism between social interaction and cognition. Married older adults are more likely than their single peers to engage in physical activity, attend routine dental visits, and limit their alcohol consumption (Watt et al., 2014). Those who were widowed had significantly higher prevalence of current smoking than those who were married or living with a partner (Watt et al., 2014). As measured by the number of social roles, social integration was associated with less age-related loss of lung function which is an important marker of health and longevity (Crittenden, Murphy, & Cohen, 2018). Similarly, social activity has been seen to independently reduce the risk of disability in older adults (James, Boyle, Buchman, & Bennett, 2011) whereas lack of social connection is strongly linked with premature

morbidity and mortality (Holt-Lunstad, Smith, & Layton, 2010). This meta-analysis found that the influence of social relationships on risk for mortality was comparable to or exceeded other well-established risk factors (e.g., obesity, physical inactivity) such that the magnitude of the effect of social relationships on mortality was comparable with quitting smoking (Holt-Lunstad et al., 2010). Further corroborating those findings was a study looking at the synergistic effect of social isolation and loneliness on mortality in middle and older adults. The study found that the higher the social isolation, the larger the effect of loneliness on mortality such that social isolation and loneliness are both important for predicting health (Beller & Wagner, 2018). There have already been clinical implications of such findings in that clinicians are being encouraged to screen for social disconnectedness as a means of addressing chronic diseases (Larrabee Sonderlund, Thilsing, & Sondergaard, 2019). Contrarily, MacNeil-Vroomen and colleagues found that older adult perception of social support was not related to longevity (i.e., time to death) after adjustment for other physical and psychological risk factors, providing contradictory evidence that perhaps social support may not have the expected impact for some individuals (MacNeil-Vroomen et al., 2018). Further research is needed in this area.

Risk of cognitive disorders

Substantial evidence supports that social activity and relationships are important for decreasing risk of dementia. Long term relationships, such as being married, have been shown to reduce the risk of dementia compared to single or widowed individuals (Sommerlad, Ruegger, Singh-Manoux, Lewis, & Livingston, 2018). Physically, socially, and cognitively stimulating leisure activities serve a protective role against dementia, and the literature suggests an added benefit with regularity of engagement over a long time span (Di Marco et al., 2014). Negative social

interactions and less community involvement have been attributed to increased risk of mild cognitive impairment and dementia. Higher baseline frequency of negative social interactions was associated with higher risk of developing mild cognitive impairment (hazard ratio = 1.53) in older adults (Wilson et al., 2015). Individuals who screened positive for MCI or dementia on the MoCA had less community involvement; however, it is unclear whether cognitive problems caused less social engagement or decreased social engagement increased risk of cognitive decline (Kotwal, Kim, Waite, & Dale, 2016). Perceived loneliness also was associated with increased risk of dementia (Sundstrom, Adolfsson, Nordin, & Adolfsson, 2020).

Social interaction and biomarkers

Similar to the other lifestyle factors, social engagement has been linked to dementia biomarkers. Much of this work has been done in rodent models using a cohousing paradigm as a proxy for human social interaction. Cohousing AD mice with wildtype mice results in increased BDNF production and neurogenesis in the hippocampus (Hsiao, Hung, Chen, & Gean, 2014), suggesting that, at least in rodents, social interaction with healthy mice promotes brain health even in diseased mice (Hsiao et al., 2014). Cohousing has also had promising results on neuroinflammation, a known contributor to the neurodegenerative process (Ardura-Fabregat et al., 2017). In another rodent study, aged mice who were cohoused (seven per cage) versus paired (two per cage) had better memory function and reduced markers of neuroinflammation (Smith, Yao, Chen, & Kirby, 2018), again suggesting social interaction is important for reducing dementia risk. Transitioning to human studies, telomere length (TL) is a robust indicator of cellular aging and TL erosion has been associated with exposure to social and traumatic stressors. Loneliness and lack of perceived social support in early adulthood may be associated

with shorter TL during transition to old age in a population that has endured extreme stress (Stein et al., 2018). Lastly, social network size modified the association between amyloid load, tau tangle density, and cognitive function (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). Even at more severe levels of global disease pathology, cognitive function remained higher for participants with larger network sizes, suggesting that social networks appear to be cognitively protective even with disease pathology present (Bennett et al., 2006).

Cognition

The cognitive benefits of social interaction are often underappreciated. Among older adults (65+), family based social capital was positively related to cognitive functioning (Sauter, Widmer, Ihle, & Kliegel, 2019). Specifically, the study found that being an active agent in one's own family (e.g., having a larger number of family members, as well as supporting them) was significantly related to enhanced cognitive performance in processing speed (Trails A), cognitive flexibility (Trails B), and vocabulary (Mill Hill Vocabulary Scale) (Sauter et al., 2019). The study suggested that active participation in social and relational tasks requires cognitive abilities but is also promoted by them (Sauter et al., 2019). Emerging literature is even exploring the concept of "relational reserve" as a parallel to cognitive reserve, with larger social and supportive family network related to a more active lifestyle and to better cognitive functioning (Sauter et al., 2020). Conversely, loneliness was found to be inversely related to general cognition, verbal memory, and processing speed at age 70 which may be in some way related to depression (Gow, Corley, Starr, & Deary, 2013). Social network was directly associated with better global cognition (adjusted z-score composite of the Digit Symbol Substitution Test, Delayed Word Recall Test, and Word Fluency Test) at baseline (ages 45–64) among Caucasians

and African American females, but curiously was not significantly associated with global cognition in African American males (Kats et al., 2016).

The role of social interaction in cognition has also been looked at longitudinally. In a population-based British cohort study, group engagement, opposed to interactions with a single individual, made a significant, sustained and unique contribution to the prediction of cognitive function four years later as measured by a factor-analysis derived generalized cognitive ability score comprised of orientation, attention, verbal fluency, verbal memory, and prospective memory measures (Haslam, Cruwys, & Haslam, 2014). Furthermore, group engagement was associated with better cognitive integrity over time (Haslam et al., 2014). It has been hypothesized that the level of engagement required to maintain group relationships is greater than that involved in maintaining individual relationships, such that this encourages greater cognitive stimulation and improved cognitive outcomes (Haslam et al., 2014), though there have also been studies suggesting significantly faster processing speed for married people compared to unmarried/singles, providing some evidence for long-term benefits of having an individual relationship (Gow et al., 2013). Haslam and colleagues found a significant interaction between group engagement and age, indicating that these group relationships matter most when people are at the older end of the age spectrum. The authors highlighted that being connected to social groups had the effect of reducing the cognitive age of an 80-year-old by 9.5 years (Haslam et al., 2014). Similar longitudinal findings of social engagement associated with better cognitive outcomes were revealed in a community cohort in Chicago. More social activity was associated with less cognitive decline during average follow-up of 5.2 years, such that a one point increase in the social activity score was associated with a 47% decrease in the rate of decline in global

cognitive function as measured by composite z-score of 19 neuropsychological tests across domains (James, Wilson, Barnes, & Bennett, 2011).

The mechanism of why and how social interaction promotes better cognition is unclear. Some suggest it is through increased cognitive activities (Brown et al., 2016), or being more socially stimulated. Loneliness has been shown to reduce social engagement, which may be caused by memory or mood problems (McHugh Power, Steptoe, Kee, & Lawlor, 2019). As mentioned previously, the mice cohousing experiment showed better memory functioning and reduced markers of neuroinflammation in mice housed with more than one other mouse (Smith et al., 2018). However, in a human study, social support and not social contact was positively associated with cognition (Gow et al., 2013), suggesting quality may be more important than quantity in humans. The exact mechanism is still uncertain. Unfortunately, people with memory problems often face more barriers to participation in social activities (Flatt et al., 2015), and thus the lack of social interaction may further perpetuate cognitive decline.

Limitations with social interaction literature

Similar limitations exist with the social interaction lifestyle behavior as with exercise and diet due to the variability of what is included in this domain. There is no established standard way to measure social interaction (Dause & Kirby, 2019), though some scholars have tried to lay out a definition to differentiate social engagement and social networks (Berkman, Glass, Brissette, & Seeman, 2000). Equally, it is hard to isolate social interaction interventions, as most social intervention protocols have an aspect of exercise or cognitive stimulation as well (Dause & Kirby, 2019). In such intervention trials, there is also the ethical dilemma of withholding

beneficial interventions from patients (Dause & Kirby, 2019) so it is sometimes hard to justify an independent "social interaction" intervention. In many of these studies, socioeconomic status is not accounted for, and if it is, participants are typically from middle to upper SES. There was a study that looked at the relationship between SES and health behaviors, and found that higher SES individuals obtained higher health behaviors scores (Watt et al., 2014), so it would be important to examine these same variables in diverse samples to see if results are generalizable. Furthermore, people who have adequate social interactions also tend to have other positive health-related behaviors such as regular exercise and more participation in cognitively enriching activities (Watt et al., 2014). Studies in this field call for rigorous clinical trials to help determine how social integration can be used to prevent cognitive decline and how that integration can be effectively and practically achieved (Dause & Kirby, 2019).

STRESS

Stress can be broadly defined as a disruption to the homeostasis of an organism (Sierra-Fonseca & Gosselink, 2018). For humans, stressors include a myriad of things like physical injuries, difficult relationships, unhealthy diet, and lack of sleep. The stress response is a series of self-regulated nervous system responses reacting to environmental, psychosocial, and other internal and external stimuli (Chrousos, 2009; Esch, Stefano, Fricchione, & Benson, 2002a). This reaction can galvanize a person into action or the opposite, cause a person to freeze and retreat. Either way, stress can be severely detrimental to health and well-being when it is chronic. Chronic stress has detrimental physiological effects on the body via dysregulated HPA axis hormone levels and has been linked to cancer (Moreno-Smith, Lutgendorf, & Sood, 2010), cardiovascular dysfunction (Esch, Stefano, Fricchione, & Benson, 2002b; Grippo & Johnson,

2009), immune system dysfunction (Khansari, Murgo, & Faith, 1990), gastrointestinal dysfunction (Soderholm & Perdue, 2001), endocrine disorders (Sapolsky, 1992), depression (Hammen, 2005), and neurodegenerative disease. In the brain, stress activates the HPA axis which causes subsequent glucocorticoid hormones (i.e., cortisol, corticosterone) to be released. This influences normal tau proteostasis, and thus disrupts neuronal structure and function, which leads to neuronal cell death and ultimately neurodegeneration (Sierra-Fonseca & Gosselink, 2018).

Stress and incidence of cognitive disorders

Onset and progression of neurodegenerative disease has been linked with chronic stress. In a community sample of older adults, high levels of perceived stress was associated with a 30% greater risk of incident amnestic MCI after three years, independent of depression, APOE ε4, and demographic factors (Katz et al., 2016). Similarly, another study of older adults who had normal cognition or MCI at baseline found that prolonged, highly stressful experiences were associated with conversion from MCI to dementia (Peavy et al., 2012). These studies suggest that preventing or reducing stress may reduce the risk of MCI onset (Katz et al., 2016) or progression to dementia (Peavy et al., 2012).

Stress and biomarkers

Stress leaves a physiological mark in the human body, regardless of age. In an MRI study of stress in younger adults, stressful stimuli resulted in decreased global network efficiency (Wheelock et al., 2018), suggesting that stress disrupts brain connectivity. In animal studies, stress has been linked with tau hyperphosphorylation and accumulation, possibly as a result of

HPA axis releasing glucocorticoids which impacts the brain (Sierra-Fonseca & Gosselink, 2018). Stress appears to be a critical factor that influences tau-mediated pathogenesis in AD and possibly other tauopathies (Sierra-Fonseca & Gosselink, 2018).

Cognition

Stress has been significantly linked to cognitive performance, both at baseline and rate of change over time. In a group of healthy older adults, worse language, episodic memory, and executive functioning were associated with increased perceived stress scores (Jiang, Seng, Zimmerman, Kim, & Lipton, 2017). The literature differentiates between subjective and objective measures of stress as they have been shown to differentially impact cognition. Perceived stress is a subjective measure of stress where the person rates how they were impacted by the stressor versus an objective measure of stress, such as physiological markers (e.g., cortisol) or the frequency (e.g., daily versus monthly) and severity (e.g., minor car accident versus the death of a child) of the event. Perceived stress scores are not strongly associated with number of stressful life events, but are associated with the personal impact of those events (Cohen, Kamarck, & Mermelstein, 1983). In a MCI population, high level of life stressors (subjective measure) predicted faster decline in cognition but high cortisol (objective measure) predicted slower decline in cognition (Peavy et al., 2009). It seems that the cognitive appraisal of the stressor determines the impact on cognition. Working memory performance was negatively impacted by stress (in a lifespan sample ages 19-83), but specifically by the perception of stress and not the total number of stressful events (Korten, Sliwinski, Comijs, & Smyth, 2014). Physical health mediated the impact of perceived stress on cognition in a sample of Chinese older adults, but overall, higher

perceived stress was associated with worse global cognition (Chen, Wang, Liang, Sun, & Dong, 2018). Subjective stress appears to have a stronger influence on cognition than objective stress.

Stress also impacts rate of cognitive decline. In a community-dwelling older adult (65+) sample, increasing levels of perceived stress (on a six-item perceived stress scale) was related to lower initial cognitive scores and a faster rate of cognitive decline (Aggarwal et al., 2014). Another study found that cognitive decline, over a two-year time period, was associated with higher global perceived stress at baseline (Munoz, Sliwinski, Scott, & Hofer, 2015). Even when controlling for age, sex, education, and vascular risk factors, higher perceived stress was significantly related to faster declines in global cognition, episodic memory, and visuospatial ability in older African American adults (mean age was 73; Turner, James, Capuano, Aggarwal, & Barnes, 2017).

Regarding demographic variables, there have been some education and gender differences. A study looking at education and effects of stress on cognition found that stressful life events predicted more rapid global cognitive decline among older adults with fewer years of education, but that stressful life events had little effect among those with more years of education (Tschanz et al., 2013). Regarding gender differences, stress appears to impact cognition differently for men and women. For example, an association between higher average cortisol levels and a worse memory on the California Verbal Learning Test has been seen in women, but not for men (Peavy et al., 2009). Similarly, cognition declines faster in women with high stress levels, than men with high stress levels, measured by cortisol (Peavy et al., 2009), though it is unclear if the cognitive change is due to psychological factors (e.g., anxiety) which have been seen to consistently

reduce cognitive functioning in older adults (Adorni et al., 2019). Regardless of the mechanism, it is important to note educational and gender differences of stress on cognition.

Limitations with stress literature

Similar to the other four lifestyle factors, there is inherent variability in measuring stress. There are differences between stress measured objectively versus subjectively, as well as notable difference in wording on the subjective stress questionnaires that have been linked to different constructs and outcomes. For example, the perceived stress questionnaire has both positively and negatively worded questions which are differentially predictive of progression from normal aging to MCI (J. M. Jiang et al., 2017). The positively worded questions have been found to measure coping ability whereas the negatively worded questions seem to measure helplessness (J. M. Jiang et al., 2017). Another study points out that when several life stressors are combined into one questionnaire, it can cancel out the effect of stress on cognition (Rosnick, Small, McEvoy, Borenstein, & Mortimer, 2007). It is possible that this is happening in many of the studies presented above, such that the authors recommend looking at each stressor individually and not combining with others (Rosnick et al., 2007).

RISK FACTORS

A comprehensive review of common risk factors associated with cognitive decline is beyond the scope of this project, however a brief overview of APOE, BMI, depression, smoking, and alcohol use is provided below.

APOE

Genetic risk factors for Alzheimer's disease and cognitive decline have been studied. The most common genetic risk factor, Apolipoprotein E, has three polymorphic alleles: ε2, ε3 and ε4, which have a worldwide frequency of 8.4%, 77.9% and 13.7%, respectively (Farrer et al., 1997). APOE effects amyloid beta metabolism, deposition, and clearance in the brain (Kim, Basak, & Holtzman, 2009). Meta-analysis of clinical and autopsy-based studies demonstrated, for Caucasians, having a copy of the ε4 allele was associated with increased risk of AD, and data suggests approximately 40% of Caucasian AD patients have a copy of ε4. The association was weaker among African Americans and Hispanics with considerable heterogeneity between the African American cohorts {Farrer, 1997 #519}. Conversely, having an ε2 allele is protective and reduces the risk of AD compared to individuals with an ε3 allele (Farrer et al., 1997; Suri, Heise, Trachtenberg, & Mackay, 2013). Individuals with ε4 exhibited a faster rate of cognitive decline compared to non- ε4 carriers (Cosentino et al., 2008). The exact mechanism of AD risk in APOE ε4+ individuals is still unresolved but thought to be from increased toxicity, loss of neuroprotection, or a combination of both (Kim et al., 2009).

BMI

Body Mass Index (BMI) is associated with increased rates of medical conditions, but also cognitive dysfunction (Buchman et al., 2005). Studies show that overweight and obese individuals have worse cognition than their healthy weight peers (Cournot et al., 2006; Kilander, Nyman, Boberg, & Lithell, 1997; Nguyen, Killcross, & Jenkins, 2014); however, some studies suggest a different pattern in older individuals. Having low BMI and losing weight puts older adults at risk for Alzheimer's disease (Shatenstein, Kergoat, & Nadon, 2001; White, 1998; Wolf-

Klein & Silverstone, 1994). Higher BMI, in some studies, has been protective of cognitive decline (Garcia-Ptacek, Faxen-Irving, Cermakova, Eriksdotter, & Religa, 2014; Memel, Bourassa, Woolverton, & Sbarra, 2016; Schmeidler, Mastrogiacomo, Beeri, Rosendorff, & Silverman, 2019), especially in women (Forte, Pesce, De Vito, & Boreham, 2017; Gustafson et al., 2012; Kim, Kim, & Park, 2016).

Alcohol

Alcohol consumption has a complex relationship with health and brain functioning. The 2015-2020 U.S. Dietary Guidelines for Americans defines moderate drinking as up to one drink per day for women and up to two drinks per day for men, though additional caution is recommended for older adults. About 40% of adults over the age of 65 drink alcohol, despite being more sensitive to alcohol, vulnerable to negative medication interactions, and at risk of exacerbating chronic health conditions. While robust evidence links chronic heavy alcohol use to brain atrophy and dementia (Topiwala & Ebmeier, 2018), moderate consumption is still under investigation. Some research touts the protective effects of moderate alcohol consumption (Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005; Stampfer, Kang, Chen, Cherry, & Grodstein, 2005); however, other studies failed to replicate the effect (Bos et al., 2017; Lobo et al., 2010; Peters, Peters, Warner, Beckett, & Bulpitt, 2008), while others linked moderate consumption with cognitive decline (Topiwala et al., 2017). In a British longitudinal cohort study of adults followed over 30 years, the authors rebuked the current U.S. alcohol consumption guidelines which posits up to 196 grams a week (i.e., fourteen drinks per week or two drinks per day) is safe for men because the study found increased odds, in a dose dependent manner, of hippocampal atrophy at just 112 grams (i.e., eight drinks) to 168 grams (i.e., twelve drinks) per

week, and no support for a protective effect of light consumption on brain structure or function as measured by a brief cognitive battery (Topiwala et al., 2017). The study found that drinking habits are typically developed in midlife and remain stable for decades, concluding that alcohol might represent a modifiable risk factor for cognitive impairment such that primary prevention interventions targeted in later life could be too late (Topiwala et al., 2017). Despite the continued controversy of alcohol's impact on cognition, alcohol consumption remains an important consideration when assessing cognition.

Depression

Depression has been inconsistently associated with cognitive functioning (Gualtieri, Johnson, & Benedict, 2006), yet remains an important variable to consider when evaluating overall health and cognition. In a review paper exploring the connection between depression and cognition, the authors acknowledged literature that linked depression to impairments in attention, learning and memory, and executive function, but added that there were disagreements about the mediators and mechanisms of cognitive impairment (McClintock, Husain, Greer, & Cullum, 2010). Similarly, there is mixed literature about the impact of depression onset and severity on cognition (McClintock et al., 2010). In older adults, the prevalence of clinically significant depressive symptoms is estimated between 8% and 16% (Blazer, 2003) and 30% in people with dementia (Lyketsos et al., 2002). Though future studies are needed to better understand the relationship between depression and cognition, assessment of depression symptoms may be important in understanding cognitive performance.

Smoking

Smoking is universally agreed to be detrimental to nearly every bodily organ (U.S. Department of Health and Human Services, 2014), including the brain, due to the abundant neurotoxic constituents (e.g., volatile organic compounds, free radicals, heavy metals, etc.), though nicotine content has been the source of some controversy. Cognition is differentially impacted by acute versus chronic nicotine use such that in nicotine naïve users, smoking may provide a cognitive boost in learning, attention, memory and executive functioning, but in chronic users may disrupt learning and memory (Campos, Serebrisky, & Castaldelli-Maia, 2016). Smoking and nicotine have been explored as they relate to neurodegenerative disorders, and some studies cite beneficial effects of nicotine, as it is the prototypical agonist of the nicotinic acetylcholine receptor, a commonly used target in several anti-dementia medications (Graham, Martin-Ruiz, Teaktong, Ray, & Court, 2002). Cochrane review of randomized control trails concluded that there was no conclusive evidence supporting the efficacy of nicotine as a treatment for Alzheimer's disease (Lopez-Arrieta, Rodriguez, & Sanz, 2000). Similarly, when nicotine is ingested via cigarettes, the toxins and smoke are associated with increased cardiovascular risk (e.g., strokes), and cortical thinning (Cho et al., 2016).

COMBINED EFFECTS

Despite well-established independent effects between cognition and lifestyle/risk factors reviewed above, few studies have taken a holistic approach and examined the combined impact of two or more healthy lifestyle factors on risk of dementia or cognitive decline. Large metanalytic and review studies conclude that single domain (e.g., diet, exercise, etc.) intervention studies are effective at reducing new incidences of AD (Xu et al., 2015), but because certain

lifestyle behaviors tend to co-occur, research studies incorporating more than one lifestyle factor reflect a more realistic perspective of a person's overall lifestyle (Mamalaki et al., 2020; Mawditt, Sacker, Britton, Kelly, & Cable, 2016). Though limited, there are some observational studies and intervention trials that have looked at the combined effects of multiple lifestyle factors (Anastasiou et al., 2018; Andrieu et al., 2017; Blumenthal et al., 2019; Bott et al., 2018; Karp et al., 2006; Li et al., 2018; Lourida et al., 2019; Mawditt et al., 2016; Ngandu et al., 2015; Norton et al., 2012; Scarmeas, Luchsinger, et al., 2009; Shakersain et al., 2018; Solomon et al., 2018; Spencer, Jamrozik, Norman, & Lawrence-Brown, 2005; Visser et al., 2019). Large observational trials collect multiple domains of data, but are subject to self-report bias and greater measurement error. Intervention trials are particularly useful because they are well controlled though sometimes lack realistic behaviors or require expensive resources, which pose challenges to generalizability. Despite all of these challenges, it is worthwhile to look at how multiple factors impact cognition and incidence of dementia especially if the combined effects of lifestyle behaviors further slow cognitive decline and/or reduce rates of dementia compared to any one lifestyle factor alone.

Previously published methods for combined lifestyle effects

Observational studies have used diverse criteria for rating lifestyle behaviors because it is challenging to combine different variables measured on different scales into a meaningful data point. The common theme between the studies is that they create some kind of hierarchy and then compare across groups. For example, when looking at specific lifestyle factors, some studies use three groups: low, moderate, and high adherence to a diet protocol (Shakersain et al., 2018), low, moderate, and intense activity for exercise (Shakersain et al., 2018), and no physical

activity, some physical activity, much physical activity for frequency of exercise (Scarmeas, Luchsinger, et al., 2009). Other studies create an overall health score or lifestyle rating score that combines multiple factors together into one number. For example, one study of Greek older adults (≥age 65 designated as normal cognition; n=1450, MCI; n=206, or dementia; n=60) derived a Total Lifestyle Index which consisted of diet, physical activity, sleep, and ADL functioning (Anastasiou et al., 2018). For each of those four factors, a score of 0 was given when the value was in the first quartile of the distribution of each specific factor and a value of 1, 2 or 3 was given when the value was within the second, third, or fourth quartile, respectively (Anastasiou et al., 2018). They then derived a sum score by adding the score of all four factors (ranging from 0-12), with higher values indicating an overall beneficial lifestyle (Anastasiou et al., 2018). In a similar approach, a lifestyle risk score was derived to predict mortality in a sample of 2,128 American adults aged 50-80 (cognition was not measured), which consisted of diet, smoking, physical activity, alcohol consumption, and BMI (Li et al., 2018). Participants scored a 1 if the factor was low risk and a 0 if it was high risk. The range was 0-5 with high scores representing lower risk lifestyle (Li et al., 2018). Another methodology, investigating health behaviors associated with mortality in 7,989 Australian men aged 65 to 83 years, was based on "prudent" lifestyle behaviors, including having either never smoked or having stopped smoking more than 1 year previously, engaging in a minimum of 3 hours of at least moderate physical activity weekly, having no more than two alcoholic drinks daily, eating fish at least three times weekly, eating meat less than five times weekly, never adding salt to food, having a self-reported body mass index (BMI) of 25.0 kg/m2 or less, and consuming reduced fat or skim milk, though no rationale was given for why these behaviors in particular were chosen (Spencer et al., 2005). Another study, consisting of 196,383 non-demented European adults over the age

of 60, incorporated both a polygenic risk score and lifestyle behavior score (consisting of no current smoking, regular physical activity, healthy diet, and moderate alcohol consumption) into three categories: favorable, intermediate, and unfavorable lifestyles (Lourida et al., 2019). In sum, there is clearly no standard way of defining healthy lifestyle, nor is there a standard way of measuring lifestyle (see **Table 2** for previously published combined effects methodologies).

Combined effects and incidence of cognitive disorders

Individuals who have healthier "lifestyle scores" have been found to have reduced risk of neurodegeneration or slowed progression of disease. In a large population-based cohort study of individuals aged 60+, a favorable lifestyle (versus intermediate or unfavorable lifestyles) was associated with a lower dementia risk among participants (Lourida et al., 2019). Cognitively normal adults with a Total Lifestyle Index score in the upper quartile had a 43% decreased odds of low cognitive performance, which is equivalent to almost three fewer years of cognitive aging (Anastasiou et al., 2018). A similar six-year follow up study looked at the types of activities that older adults engaged in and found lower relative risk of dementia in non-demented older adults who engaged in activities that incorporated physical, mental and social aspects with the most beneficial effect seen for participants with high scores in two or more of the components (Karp et al., 2006), further supporting the beneficial impact of multiple healthy behaviors.

Combined effects and biomarkers

Lifestyle interventions and higher scores on healthy lifestyle indexes have been shown to reduce the risk of AD despite genetic predisposition. In a population-based cohort of individuals over age 60, a favorable lifestyle was associated with a lower dementia risk even among participants

with a high genetic risk of developing AD, suggesting that despite genetic predisposition, a healthy lifestyle was protective of decline (Lourida et al., 2019). Similarly, a multi-faceted lifestyle intervention afforded similar benefits to APOE ε4 + individuals and those without the AD genetic risk (Solomon et al., 2018). The combined effect of multiple lifestyle factors with other biomarkers (e.g., cortical thickness, hippocampal volume, glucose uptake, amyloid deposition, etc.) is lacking. Most studies involving biomarkers look at lifestyle factors individually. For example, one study of older adults with subjective cognitive complaints or mild cognitive impairment underwent PET scans to understand the relationship between deposition of amyloid and tau (measured via 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile; FDDNP) with BMI, Mediterranean diet adherence, and self-reported physical activity (Merrill et al., 2016). Though all three of these lifestyle variables were examined in the same study, their relationship with FDDNP was examined individually (Merrill et al., 2016). Elevated levels of FDDNP binding corresponded with more pathology. Results revealed that MCI subjects with normal BMI had less FDDNP binding than individuals with overweight/obese BMI; MCI subjects who engaged in greater physical activity had less FDDNP binding compared to MCI subjects with less physical activity, and healthier diet, regardless of cognitive status, was related to lower FDDNP binding (Merrill et al., 2016). Future studies are needed to examine the effects of multiple lifestyle factors together on brain-based biomarkers.

Cognition

A healthy lifestyle positively impacts both global cognition and specific cognitive domains. Positive associations were found between the Total Life Index and memory, executive functioning, visuospatial abilities, and language domains, but not for attention and processing

speed (Anastasiou et al., 2018). Another study found improvements in a combined score of Trail Making Test, Digits Forward and Backwards, Stroop, Coding, Ruff 2 Naming, and Category Fluency, with a combination of aerobic exercise and DASH diet intervention (Blumenthal et al., 2019). Similar results were found observationally: moderate-to-high adherence to the Nordic dietary pattern was associated with less decline in MMSE scores over time, but the association was stronger when combined with moderate-to-intense physical, mental, or social activities (Shakersain et al., 2018). The authors concluded that an active lifestyle strengthened the effect of healthy dietary pattern on cognitive function by two times, and further lowered risk of MMSE decline by 30% (Shakersain et al., 2018). Thus, an active lifestyle reinforces the effect of a healthy diet on cognitive function, and further decreases the risk of cognitive decline.

Additional studies support the same overall pattern of findings of additive effects of multiple lifestyle factors. A graded relationship was observed between a greater number of healthful lifestyle factors (high vegetable intake, high fish intake, high physical activity, no current smoking, light to moderate alcohol consumption) and less decline in global cognition and story memory over a two-year period after adjusting for covariates (Weng et al., 2018). In a randomized control trial looking at DASH diet and aerobic exercise for six months in sedentary older adults with cognitive complaints but no dementia, the largest cognitive improvements were observed for participants randomized to the combined aerobic exercise and DASH diet group compared to the control group (Blumenthal et al., 2019). Similarly, in a two-year Finnish lifestyle intervention trial of at-risk older adults, those who were randomized into the intervention group, where they got dietary, exercise, and cognitive training along with vascular risk monitoring, were found to have significantly higher global cognition composite scores than

the control group, with the largest differences in executive functioning and processing speed (Ngandu et al., 2015). Executive functioning and processing speed along with verbal memory were also influenced by the combination of healthier diet (DASH) and increased physical activity (more steps on pedometer) (Blumenthal et al., 2017).

Limitations with combined effects literature

Though many studies support the idea that multiple lifestyle factors have combined effects on cognition and dementia, a relationship is not always found. Due to the variability in study design and variable measurement, it is difficult to know if these are genuine negative findings or instead due to methodological problems. For example, one multidomain intervention study found that polyunsaturated fatty acid supplementation, either alone or in combination with healthy diet, physical activity, and cognitive training interventions, had no significant effects on cognitive decline over three years in elderly people with memory complaints (Andrieu et al., 2017). These findings suggest opposite results compared to most studies, but the participants may have been too cognitively impaired to see benefit, the protocol may not have been the right type of intervention, or the time frame was not sufficient to see change. Intervention studies presented in the literature are often too short to know the true long-term effects of such intervention. For example, a diet and exercise randomized control intervention trial found benefits at six months (Blumenthal et al., 2019); however, it would be interesting to know the effects one, five, and ten years later. When studies do span a significant amount of time, adherence can become a problem, especially when older adults, who may have a memory impairment, are asked to deviate from routine and implement a new dietary regimen or exercise protocol. Despite these concerns,

studies have published adequate adherence in memory compromised cohorts (Blumenthal et al., 2019).

Another limitation is often the quality and quantity of the data. A few multi-domain lifestyle factor studies have been limited by minimal cognitive data (Scarmeas, Luchsinger, et al., 2009; Shakersain et al., 2018) whereas others have been limited to only one or two lifestyle factors (Blumenthal et al., 2019; Rege, Geetha, Broderick, & Babu, 2017). Others are exclusively cross-sectional (Anastasiou et al., 2018). Many studies do not provide rationale for why certain factors are included in the Health Score and others focus on risk behaviors instead of health behaviors, which may have a different relationship to cognition. A further complicating matter is that a vast majority of the published lifestyle studies are performed outside of the United States or come from non-American cohorts. For whatever reason, lifestyle related studies are more prominent in other countries including Sweden (Karp et al., 2006; Shakersain et al., 2018), Finland (Ngandu et al., 2015), China/Taiwan (Weng et al., 2018), Canada (Hersi et al., 2017), Australia (Spencer et al., 2005), Greece (Anastasiou et al., 2018), and France, (Andrieu et al., 2017; Feart et al., 2009) to name a few, with unclear generalizability to American samples. Lastly, research involving combined lifestyle factors is still a relatively novel paradigm and still in the stage of optimizing adherence and refining study designs. Despite being a relatively new area, there is a need for large, multi-domain studies to elucidate the complex relationship between lifestyle behaviors and cognitive health. Studies specifically designed to measure the impact of healthy diet, regular exercise, adequate sleep, social interaction and stress management behaviors on cognitive aging are particularly necessary.

SUMMARY AND CASE FOR CURRENT PROJECT

Overall, there is a wealth of literature looking at individual lifestyle factors (i.e., diet, physical activity, sleep, social interaction, stress) or risk factors (i.e., APOE status, depression, smoking, alcohol consumption) and aspects of brain health (e.g., incidence of dementia, biomarkers, cognition, etc.). Though measurement of each factor is heterogeneous, the preponderance of results supports unique contributions of each healthy lifestyle behavior on brain health. However, there are few studies that look at multiple lifestyle factors together. The goal of the current study was to advance the literature by examining several healthy lifestyle factors and risk factors together to determine whether a combination of multiple factors could better predict cognition and rate of decline in older adults. This study helps to determine the impact of health behaviors on cross-sectional and longitudinal cognition, inform patient care, and guide future research.

CHAPTER THREE: Aims & Hypotheses

AIM 1

To determine which lifestyle factors best predict cognition cross-sectionally.

Hypothesis 1: There will be more than one lifestyle factor that significantly predicts global cognition. Specifically, more physical activity, more social activities, and less sleep fragmentation will be significant predictors of better cognition.

Hypothesis 2: Physical activity (measured by actigraphy) will be a significant predictor in each of four cognitive domains (i.e., global cognition, verbal memory, processing speed, working memory). Specifically, higher physical activity will be associated with better cognition in each domain.

Hypothesis 3: Diet (measured by MIND adherence) will be a significant predictor of verbal memory. Specifically, better diet adherence will be associated with better verbal memory.

AIM 2

To derive and compare different approaches to developing cross-sectional Health Scores (HS) that best predict global cognition at analytic baseline.

Hypothesis 4: A Health Score incorporating lifestyle factors and risk factors will outperform a Health Score with fewer factors in predicting global cognition.

Hypothesis 5: Health Scores incorporating lifestyle factors will better predict cognition than Health Scores incorporating risk factors alone.

AIM 3

To understand the relationship between overall health (i.e., Health Score) and rate of cognitive change in each of four cognitive domains.

Hypothesis 6—Global Cognition: There will be a statistically significant difference between rates of change in global cognition in individuals with Health Scores in the highest versus the lowest quartile. Specifically, a higher Health Score will be associated with a slower rate of cognitive decline.

Hypothesis 7—Verbal Memory: There will be a statistically significant difference between rates of change in verbal memory in individuals with Health Scores in the highest versus the lowest quartile. Specifically, a higher Health Score will be associated with a slower rate of cognitive decline.

Hypothesis 8—Processing Speed: There will be a statistically significant difference between rates of change in processing speed in individuals with Health Scores in the highest versus the lowest quartile. Specifically, a higher Health Score will be associated with a slower rate of cognitive decline.

Hypothesis 9—Working Memory: There will be a statistically significant difference between rates of change in working memory in individuals with Health Scores in the highest versus the lowest quartile. Specifically, a higher Health Score will be associated with a slower rate of cognitive decline.

CHAPTER FOUR: Method

Rush University Medical Center's NIA-funded Alzheimer's Disease Center Memory and Aging Project (MAP) is a longitudinal, epidemiologic clinical-pathologic cohort study of common chronic conditions of aging with an emphasis on decline in cognitive and motor function and risk of Alzheimer's disease (Bennett et al., 2012). The MAP study began in 1997 with the goal of identifying postmortem indices linking genetic and environmental risk factors to the development of AD in the hope that such information would help provide a basis for rational nonpharmacologic and pharmacologic strategies to prevent AD (Bennett et al., 2005). As such, longitudinal lifestyle variables were prioritized in data collection. During annual visits, participants underwent detailed assessment of risk factors, blood donation, and detailed clinical evaluation.

PARTICIPANTS

Participants in the larger study were primarily recruited from continuous care retirement communities and churches. In order to increase diversity of the cohort, recruitment efforts additionally occurred in areas with subsidized housing and agencies serving minorities and low-income elderly. Exclusion criteria were minimal and included first, that they did not have a known dementia diagnosis and second, that they understood the study included the Anatomical Gift Act (i.e., the donation of their brain, spinal cord, as well as selected nerves and muscles at the time of death). The individuals in the cohort were not excluded based on common health infirmities at baseline as the goal was to capture a community sample and minimize the healthy volunteer effect. In total, the overall sample consisted of 2,133 participants. For the present study, individuals with less than all five lifestyle variables (i.e., diet, physical activity, sleep

fragmentation, social activities, perceived stress) and/or missing cognitive data were excluded (n=1,666) resulting in 467 participants for the present study (see Figure 1).

MEASURES

Of the comprehensive array of medical, psychological, physiological, and demographic information available in the Rush study, the current project included four categories: cognition, healthy lifestyle behaviors, risk factors, and demographics. Cognition slopes and Health Scores were calculated specifically for this project and were not provided from the Rush database. Regardless of study entry date, the current study utilized data from each participant's "analytic baseline," defined as the first visit in which the participant had all variables of interest. The term "analytic baseline" will be used throughout to denote this time point.

Cognition

The Rush cognitive battery was comprised of twenty-one tests, nineteen of which were included in this study to assess five cognitive domains (**Table 3**). The remaining two tests included the MMSE (Folstein, Folstein, & McHugh, 1975) and Complex Ideas from the Assessment of Aphasia and Related Disorders (Goodglass & Kaplan, 1972) which were used to describe the sample and for diagnostic purposes. Individual tests within each domain are listed below.

Episodic memory (7 measures): Measures included immediate and delayed recall of Story A from the Wechsler Memory Scale – Revised Logical Memory subtest (Wechsler, 1987) and of the East Boston Story (Albert et al., 1991; Wilson et al., 2002), and Word List Memory, Word List Recall, and Word List Recognition from the Consortium to Establish a Registry for

Alzheimer's Disease (CERAD; Morris et al., 1989). Episodic memory was referred to as "Verbal Memory" for the current project.

Semantic memory (3 measures): 15-item Boston Naming Test (Morris et al., 1989), (Kaplan, Goodglass, & Weintraub, 1983), Verbal Fluency (Categories: Animals & Fruits/Vegetables; Morris et al., 1989; Wilson et al., 2002), and a 15-item reading test (Wilson et al., 2002).

Working memory (3 measures): Digit Span Forward and Digit Span Backward (WAIS-R; Wechsler, 1987)
and Digit Ordering (Cooper & Sagar, 1993; Wilson et al., 2002).

Perceptual speed (4 measures): Symbol Digit Modalities Test (Smith, 1984), Number Comparison (Ekstrom, Dermen, & Harman, 1976; Wilson et al., 2002), and two indices from a modified version of the Stroop Neuropsychological Screening Test (the number of color names correctly read aloud in thirty seconds minus the number of errors, and the number of colors correctly named in thirty seconds minus the number of errors) (Trenerry, Crosson, DeBoe, & Leber, 1989). This domain was referred to as "Processing Speed" for the current project.

Visuospatial ability (2 measures): 15-item version of Judgment of Line Orientation (Benton, Varney, & Hamsher, 1978), and a 16-item version of Standard Progressive Matrices (Raven, 1992)

Composite scores: The five cognitive domains (i.e., Verbal Memory, Semantic Memory, Working Memory, Processing Speed, and Visuospatial Ability) were derived via the convergence of hypothesized groupings and empirical groupings which were calculated from principal-component factor analysis with varimax rotation (Wilson, Barnes, & Bennett, 2003; Wilson et al., 2002). Each domain score was derived by converting raw scores from each test into a z-score, using the baseline mean and standard deviation, and then averaging the z-scores of the tests within each domain (Wilson et al., 2002). If a test was missing, the domain score was not calculated unless at least half of the tests within the domain had scores present, in which case the composite score was based on the available test scores (Wilson et al., 2002). A composite measure of Global Cognition was derived by averaging the z-scores of all tests as previously described (Bennett et al., 2005; Wilson et al., 2003). This value was calculated only if more than half of the nineteen neuropsychological tasks were collected.

Cognitive rate of change (Cognition Slope): This variable was calculated for participants with three or more years of complete lifestyle and cognition data. Cognition rate of change (Cognition Slope) was calculated in Excel using the SLOPE function which derived the slope of the regression line using visit year on the x-axis and the corresponding cognition z-score score on the y-axis. Cognitive slopes that were greater than 3.5 standard deviations from the mean were excluded. This variable was calculated specifically for this study and was not provided by the Rush database.

Healthy Lifestyle Factors

Overview: The specific variables chosen to represent each lifestyle domain in the present study were chosen intentionally. There have been many (about 40) prior studies published from this Rush cohort examining one healthy lifestyle factor (e.g., diet) and brain-health outcomes (e.g., risk of AD or cognitive score). Many Rush studies examined the effect of one lifestyle domain using several different variables to see which had the strongest relationship to the desired brain health outcome. The variable that was determined to have the strongest association was intentionally chosen for the current study. For example, in a study looking at multiple diet scores associated with cognition and rate of cognitive change (i.e., DASH diet, Mediterranean diet, and MIND diet), the MIND diet had a stronger association and was a better predictor of cognitive change than the other two diet scores in the study (Morris et al., 2015). Therefore, the MIND diet was selected as the variable to represent the "Diet" lifestyle factor for the current project. Similar papers were published for each of the other four lifestyle domains and are outlined below. Lifestyle variables were measured annually as part of the participants' comprehensive visit.

Diet: Diet was measured using a food frequency questionnaire (FFQ) where participants recorded their usual frequency of intake of 144 food items over the previous 12 months. Items included vitamins and mineral supplements, beverages, dairy products, main dishes, miscellaneous foods, bread and cereals, fruits and vegetables, and snack foods/desserts. The FFQ was analyzed and broken down into an interpretable report which included nutrient levels and total energy of each food item based either on natural portion sizes or according to age-specific portion sizes from national dietary surveys. From that report, a MIND diet score was derived from a summation of 15 diet components including healthy (e.g., vegetables, olive oil, fish, etc.)

and unhealthy foods (e.g., fried food, pastries, etc.; see **Appendix A** for full description). Each diet component was scored as 0, 0.5 or 1 based on frequency of consumption of that proportion. The total MIND diet score ranged from 0 to 15 with higher scores indicating greater diet concordance. The MIND diet was chosen as the "Diet" variable because it had a stronger association with cognition and was a better predictor of cognitive change than the DASH and Mediterranean diet scores (Morris et al., 2015).

Physical Activity: Average total daily activity was measured via a portable actigraph (Phillips Respironics, Bend, OR) worn by participants for ten consecutive days; they were asked to keep the device on their person at all times. The Actical was a wristwatch-like accelerometer that continuously measured acceleration worn on the individual's non-dominant hand. Average daily activity scores were calculated by summing the activity during each 24-hour period and averaging it across the ten days of data collection (or the number of days that the individual wore the Actical if less than ten). Total count was divided by 100,000 to facilitate presentation and interpretation of the results. The average daily activity score included exercise-related and non-exercise-related physical activity. Higher levels of daily physical activity have been associated with a reduced risk of AD in the Rush sample (Buchman et al., 2012). The average total daily activity was chosen as the "Physical Activity" variable because it was the objective measure of physical activity available in the Rush database and has been found to be associated with the Global Cognition composite, whereas a self-report measure of physical activity was not associated with cognition (Buchman et al., 2012; Buchman et al., 2008).

Sleep Fragmentation: Sleep fragmentation is a measure of transitioning from a state of rest to a state of activity and was measured via the same actigraph used to collect the physical activity data (Phillips Respironics, Bend, OR). The actigraph was worn by participants for ten consecutive days but periods of four straight hours of complete inactivity was suspect for device removal and thus the full day (24-hour period) was excluded from analyses (Lim, Kowgier, et al., 2013). The device recorded activity counts for 1-second samples and then summed the counts into 15-second intervals called epochs. Each epoch was classified as resting (zero counts per epoch) or active (greater than zero counts per epoch). Runs of rest began with at least one epoch of rest and ended at the epoch before the first epoch of activity. Each run of rest began with an activity-to-rest transition and ended with a rest-to-activity transition. kRA was derived in prior Rush studies (Lim et al., 2011; Lim et al., 2012) and is the nomenclature used to represent the probability per epoch of having an arousal, as indicated by movement (i.e., a non-zero activity count), after a long (about five minute) period of rest (i.e., sleep). The higher the kRA the more quickly bouts of sleep/rest end in arousals and hence the greater the degree of sleep fragmentation (Lim, Kowgier, et al., 2013). kRA was calculated from the entire 24-hour period and captured sleep fragmentation both during day and night (i.e., daytime naps and nighttime sleep), though kRA was most heavily influenced by the time period in which the greatest amount of sleep occurs, which for most individuals was the night (Lim, Kowgier, et al., 2013). For comprehensive explanation of kRA calculation see (Lim et al., 2011). Overall, higher values of kRA represent more disrupted sleep and lower values of kRA represent more uninterrupted sleep. The kRA variable was chosen as the "Sleep" variable because high kRAs were associated with an increased risk of AD and faster rate of cognitive decline compared to low sleep fragmentation in the Rush sample (Lim, Kowgier, et al., 2013). kRA was also chosen because it

is an objective sleep measure, and not a subjective sleep measure like the Pittsburg Sleep Quality Index, as subjective sleep measures have not consistently been associated with cognition (Blackwell et al., 2011).

Social Activities: Social activity was assessed using a 6-item scale (Mendes de Leon, Glass, & Berkman, 2003; Wilson et al., 2007) that asked how often during the past year participants engaged in common types of activities that involved social interaction (**Appendix B**). Each item was rated on a 5-point scale with higher values indicating more frequent participation. Item scores were averaged to yield the composite score which ranged from 0 to 30. Higher scores indicated more frequent social activity. The Social Activities variable was chosen as the "Social" variable because a previously published Rush paper suggested that socially active older adults experience less cognitive decline in old age compared to their less frequently socially active peers (James, Wilson, et al., 2011). The Social Activities variable, as opposed to other social-related variables in the Rush ADC, was chosen because Social Activity was related to cognition, but social network size was not (Krueger et al., 2009). Social support was related to cognition, but access to that social variable was unavailable.

Perceived Stress: Perceived stress was measured annually via self-report questionnaire asking about the past month. The questionnaire used was the 4-item Cohen's Perceived Stress Scale (PSS), which is an index of the degree to which a person finds their life "unpredictable, uncontrollable, and overloading." Unlike many of the other self-report measures used in the present study, this perceived stress scale was not modified from its original form when incorporated into the Rush study; therefore, reliability and validity data from other studies can be

examined. The 4-item PSS was determined to have adequate internal reliability (r = 0.6) in an adult population and correlated more closely with questions asking about the past week than the prior year. Regarding construct validity, higher scores on the PSS were correlated with worse perceived health status and higher rates of serious illness but the PSS was only slightly related to health behaviors (i.e., higher PSS associated with less sleep, infrequent breakfast consumption, increased alcohol consumption, and increased usage and frequency of drugs; Cohen & Williamson, 1988). PSS was inversely related to life satisfaction.

Participants were asked to rate the frequency at which they perceived stress in the past month using a 5-point rating scale (**Appendix C**). The overall score ranged from 0 to 4 and was the average of the individual item scores, with higher scores indicating greater levels of perceived stress. The Perceived Stress variable was chosen as the "Stress" variable because higher levels of perceived stress were associated with more rapid decline in Global Cognition compared to lower levels of perceived stress in African Americans from Rush's Minority Aging Research Study (Turner et al., 2017).

Risk Factors

Alcohol Consumption: Alcohol use was measured at study entry via an alcohol questionnaire inquiring about annual alcohol use. From that questionnaire, daily grams of alcohol were calculated for each individual. Totals ranged from 0 to 234.6 grams, with higher values indicating greater alcohol consumption. For reference, 14 grams is approximately equal to a standard drink.

Smoking Status: Smoking status was assessed at study entry and categorized as current smoker, former smoker, or never smoker.

Depression Symptoms: Depression was measured using a modified, 10-item version of the Center for Epidemiologic Studies Depression scale (CES-D; **Appendix D**) based on the individual's experience of ten symptoms over the past week. The total score ranges from 0-10 and represented the number of endorsed symptoms. Prior studies have found good sensitivity, specificity, and positive predictive value using a cutoff score of ≥ 4 in older adults (Irwin, Artin, & Oxman, 1999; Kohout, Berkman, Evans, & Cornoni-Huntley, 1993).

APOE ε4 Status: APOE genotyping was derived from serum analysis and the two-allele combination was recorded for each participant. APOE ε4 status was treated as a categorical variable (i.e., 0, 1 or 2 copies of the ε4 allele) for the regression analyses.

Body Mass Index: BMI was calculated using the formula of weight in kilograms divided by height in meters squared. The Center for Disease Control categorizes BMI as underweight, healthy weight, overweight, class 1 obesity, class 2 obesity, and class 3 obesity. These categories were set at BMI less than 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, 35 to 40, greater than 40, respectively.

Health Scores

In order to assess the combined effects of multiple factors, four "Health Scores" were derived. The Health Scores were not in the Rush database but were calculated specifically for this project

based on each participant's analytic baseline. First, lifestyle factors and risk factors were assigned point-values where, in general, higher values correspond with greater health. Second, Health Scores were derived based on *a-priori* combinations. Third, Health Scores were assigned categories.

Point-value assignment: A score of 4, 3, 2, and 1 was assigned for values in the fourth, third, second, and first quartile for Diet, Physical Activity, and Social Activities. Sleep Fragmentation and Perceived Stress were negatively oriented (i.e., higher scores indicated worse sleep and more stress) and treated differently. For Sleep Fragmentation, scores of 4, 3, 2, and 1 were assigned for values in the first, second, third, and fourth quartile, respectively. For Perceived Stress, due to the narrow range of raw scores, points were assigned based on the measure's raw summary score. Raw scores between 0 to 0.9, 1 to 1.9, 2 to 2.9, and 3 to 4 were assigned 4, 3, 2, and 1 points, respectively. Due to the limited distribution of alcohol consumption, a score of 4 was assigned to those who did not drink alcohol (0 grams), a score of 3 was assigned to those who had on average less than one drink per day (0.01 to 13.99 grams), a score of 2 was assigned to those who had one to two drinks per day (14 to 28 grams), and a score of 1 was assigned to individuals consuming more than two drinks per day (>28 grams). For depression, a score of 4, 3, 2, or 1 was assigned for CES-D scores ranging from 0, 1-3, 4-6, and 7-10, respectively. For smoking, due to the limited categories, 2 points was not assigned. However, a score of 4 was assigned to "never smoker," 3 was assigned to "past smoker," and 1 was assigned to "current smoker." APOE combinations were allocated points based on odds ratios of developing Alzheimer's disease (Farrer et al., 1997). Four points were assigned to ε2/ε2 and ε2/ε3, 3 points were assigned to ε3/ε3, 2 points were assigned to ε2/ε4 and ε3/ε4, and 1 point was assigned to

ε4/ε4. Regarding BMI, 4 points were assigned to Healthy Weight (BMI: 18.5 to 24.9), 3 points were assigned to Underweight (BMI: < 18.5) and Overweight (BMI: 25 to 29.9), 2 points were assigned to Class 1 Obesity (BMI: 30 to 34.9), and 1 point was assigned to Class 2 (BMI: 35 to 39.9) and Class 3 (BMI: 40+) Obesity. See **Table 4** for a visual representation of point-value assignment.

A-priori Health Score Combinations: The Health Scores (HS) are summary scores, where higher scores indicate greater health. Four Health Score groupings were selected in order to capture different approaches to combining factors into a composite score (**Table 5**). Specifically, HS1 takes a scientific approach and includes the significant predictors identified in Aim 1. HS2 takes a lifestyle/health approach and includes the five lifestyle factors (i.e., Diet, Physical Activity, Sleep Fragmentation, Social Activities, Perceived Stress). HS3 takes a risk/disease approach and includes the five risk factors (i.e., alcohol use, depression symptoms, smoking status, APOE ε4 status, BMI). Lastly, HS4 takes a comprehensive approach and includes all five lifestyle factors and all five risk factors.

Averaged Health Score: As a hypothetically more stable measure of lifestyle behaviors, an Averaged Health Score was derived. This score was derived for individuals with three or more years of complete lifestyle and cognition data. The Averaged Health Score was calculated by summing the Health Scores derived at each visit and then dividing by the number of visits with available data.

Health Score Categories: Health Scores were designated as “Favorable,” “Moderately Favorable,” “Minimally Favorable,” and “Unfavorable” corresponding with the fourth, third, second, and first quartile, respectively.

Demographics

Demographic factors known to have associations with cognition were examined in this study and included age, education, sex, early life socioeconomic status (SES), and diagnosis all at analytic baseline.

Age: Age was documented at each visit. In analyses incorporating multiple time points, the age at analytic baseline was used.

Education: Years of education was measured as the number of years of regular school reported at study entry. Education was capped at 20 years.

Sex: Participants’ sex was recorded as either male or female. For all analyses, males were coded as 1, females were coded as 0.

Early Life Socioeconomic Status (SES): This variable is a composite index based on three indicators of household SES including paternal education (in years), maternal education (in years), and number of children in the family. Maternal and paternal education variables were converted into z-scores. The number of children was multiplied by -1 and then converted into a z-score. Finally, the three z-scores were averaged to create the composite measure of early life

SES. Prior studies noted early life SES is associated with late-life cognition, but not rate of cognitive decline or risk of AD (Wilson et al., 2005).

Diagnosis: Diagnoses were rendered at every study visit but the diagnosis at analytic baseline was used in the present study. Though a dementia diagnosis was an exclusion criterion at study entry, some individual did have an AD diagnosis at analytic baseline and were not excluded from the present study in order to capture cognitive variability in this aging sample. Diagnoses were determined based on cognitive test scores (i.e., 19 neuropsychological tests), a neuropsychologist's designation of impairment, and a clinician's (i.e., neurologist, geriatrician, or geriatric nurse practitioner) review of all available data. Clinical diagnosis of dementia and clinical Alzheimer's dementia were based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA; McKhann et al., 1984). The diagnosis of Alzheimer's dementia required evidence of a meaningful decline in cognitive function relative to a previous level of performance with impairment in memory and at least one other area of cognition. Diagnosis of mild cognitive impairment (MCI) was rendered for persons who were judged to have cognitive impairment by the neuropsychologist but were judged to not meet criteria for dementia by the physician. Persons diagnosed with MCI or Alzheimer's dementia could also be diagnosed with another condition that contributed to their cognitive impairment (MCI+ or AD+), but for the present study, these individuals were combined into the MCI and AD group, respectively. Persons without dementia or mild cognitive impairment were categorized as having no cognitive impairment (NCI). The above variables were coded as follows: NCI=1, MCI=2, AD=3.

DATA ANALYSIS

All analyses were calculated using Microsoft Excel version 16.30 and SPSS version 26. Statistical significance was set at $p<.05$ unless otherwise noted. Power analyses were conducted using Power Analysis and Sample Size Software (PASS, 2019).

Aim 1

To determine which factors best predict cognition, all factors including lifestyle factors (i.e., diet, physical activity, sleep, social activities, and perceived stress), risk factors (i.e., alcohol use, smoking status, BMI, APOE ε4 status, and depression symptoms) and demographic factors (i.e., age, education, sex, early life SES, and diagnosis) were entered into separate stepwise multiple linear regression analyses predicting each cognitive domain (1-global cognition, 2-verbal memory, 3-processing speed, 4-working memory) at first year of available data.

Aim 2

To derive and compare different approaches to developing cross-sectional Health Scores that best predict global cognition at analytic baseline, multiple linear regression analyses were performed for each of the four Health Scores, predicting global cognition. Demographic variables at analytic baseline (i.e., age, education, sex, early life SES, diagnosis) were included as covariates. The models were compared using Meng's Test of Two Correlated Correlations to determine which approach (i.e., which Health Score) best predicted cognition. Meng's Test detects significant differences between two models, but R-squared values and beta weights were additionally examined to determine the "best" approach to predicting cognition.

Aim 3

The Health Score determined to be the best cross-sectional predictor of cognition in Aim 2 was categorized on the Favorable to Unfavorable scale. A between subjects one-way analysis of covariance (ANCOVA) analysis was performed to determine differences in rate of cognitive change between the Health Score categories. A second analysis was performed using the Averaged Health Score. These two analyses were performed for each of the four cognitive domains.

CHAPTER 5: Results

SAMPLE CHARACTERISTICS

A total of 467 participants with available data for all five lifestyle variables at a single time point were included in this study. For participants who had all five lifestyle factors at multiple time points, the first time point with data was used as their analytic baseline. On average, the sample was mostly white (95%), female (73%), highly educated (M_{edu}; SD= 15 years; 2.7), non-cognitively impaired (NCI; 77%) older adults (M_{age}; SD= 83; 7.1). There were n=361 NCI, n=94 (20% of the overall sample) with MCI and n=12 (3% of the overall sample) with AD (Figure 1). The MCI and AD groups combined into an "Impaired" group were on average 5 years older than the NCI group (M_{age}: 87 vs 82 years) but were included in the analyses to increase sample size and compare diagnostic groups. The overall sample had low depression scores ($M_{CES\text{-}D}$; SD =1.04; 1.63), low alcohol consumption ($M_{alcohol(g)}$; SD = 6.02; 13.6), relatively few current smokers (<3%), and an average BMI in the overweight range (M_{BMI}; SD= 26.7; 5.2). Diet, physical activity, social interaction, sleep fragmentation, and perceived stress had mean and standard deviations as follows: diet= 7.6 (1.9); physical activity= 2.7 (1.5); sleep fragmentation= 0.030 (0.007); social activities= 2.57 (0.60); perceived stress= 2.07 (0.46). Regarding cognition, all domains had a positive z-score (Mean (SD); global cognition= 0.13 (0.56); verbal memory= 0.25 (0.73); processing speed= 0.03 (0.79)) except for Working Memory (0.002 (0.73)). See **Table 6** for full demographic descriptive data.

AIM 1 REGRESSION RESULTS

Stepwise multiple linear regression was performed to determine which factors significantly predicted cognition. For each cognitive domain, all demographic variables (i.e., age, education, sex, early life SES, diagnosis), risk factors (i.e., APOE ε4 status, depression symptoms, alcohol, smoking, BMI), and lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, and perceived stress) were entered into the model. In the initial stepwise model for each cognitive domain, predictors significant at $p<0.2$ were included as potential variables in the final model. The final models included only the factors significant at $p<0.05$. Diagnosis was an ordinal variable coded as 1= no cognitive impairment, 2=MCI, 3=AD. Males were coded as 1, females were coded as 0.

Global Cognition

The final model for global cognition resulted in an R_2 of 0.542 and an Adjusted R_2 of 0.537 ($F(5, 461)=109.15$; $p< 0.001$). Significant predictors ($p<.05$) included age (B= -0.019; 95% CI: -0.024 to -0.013), education (B= 0.060; 95% CI: 0.047 to 0.073), sex (B= -0.152; 95% CI: -0.231 to -0.072), social activities (B= 0.077; 95% CI: 0.015 to 0.0139), and diagnosis (B= -0.580; 95% CI: -0.655 to -0.505). Higher global cognition was significantly predicted by younger age, more education, female sex, more social activities, and "no cognitive impairment." The initial model is presented in **Table 7** and the final model is presented in **Table 8**.

Verbal Memory

The final model for verbal memory resulted in an R_2 of 0.478 and an Adjusted R_2 of 0.473 ($F(4, 461)= 105.46$; $p< 0.001$). Significant predictors ($p< 0.05$) included age (B= -0.019; 95% CI: -0.026 to -0.012), education (B= 0.055; 95% CI: 0.037 to 0.072), sex (B= -0.297; 95% CI: -0.405

to -0.186), and diagnosis (B= -0.801; 95% CI: -0.902 to -0.700). Higher verbal memory was significantly predicted by younger age, more education, female sex, and "no cognitive impairment." The initial model is presented in **Table 9** and the final model is presented in **Table 10**.

Processing Speed

The final model for processing speed resulted with an R_2 of 0.339 and an Adjusted R_2 of 0.330 ($F(6, 452)= 38.56$; $p< 0.001$). Significant predictors ($p< 0.05$) included age, (B= -0.031; 95% CI: -0.040 to -0.022), education (B= 0.045; 95% CI: 0.023 to 0.067), sex (B= -0.206; 95% CI: -0.343 to -0.069), depression (B= -0.046; 95% CI: -0.084 to -0.009), social activities (B= 0.168; 95% CI: 0.061 to 0.275), and diagnosis (B= -0.488; 95% CI: -0.619 to -0.357). Faster processing speed was significantly predicted by younger age, more education, female sex, less depression symptoms, more social activities, and "no cognitive impairment" diagnosis. The initial model is presented in **Table 11** and the final model is presented in **Table 12**.

Working Memory

The final model for working memory resulted with an R_2 of 0.178 and an Adjusted R_2 of 0.171 ($F(4, 457)= 24.75$; $p< 0.001$). Significant predictors ($p< 0.05$) included education (B= 0.045; 95% CI: 0.020 to 0.069), early life SES (B= 0.108; 95% CI: 0.015 to 0.201), diet (B= 0.036; 95% CI: 0.003 to 0.070), and diagnosis (B= -0.445; 95% CI: -0.573 to -0.318). Higher working memory was significantly predicted by more education, higher early life SES, higher diet adherence, and "no cognitive impairment" diagnosis. The initial model is presented in **Table 13** and the final model is presented in **Table 14**.

Post Hoc Aim 1 Exploratory Results

Given the consistent, and not surprising, relationship between cognition and diagnosis, post-hoc analyses were performed to explore the predictive abilities of demographic, lifestyle and risk factors on global cognition, the other cognitive domains were not analyzed, for the non-impaired group (NCI) and the impaired group (MCI and AD) separately. For the NCI group (n=357), the significant factors predicting global cognition were very similar to that of the full sample analysis for global cognition. The final model for the NCI group resulted in a R_2 of 0.305 and an Adjusted R_2 of 0.295 ($F(5, 351)=30.84$; $p< 0.001$). Significant predictors ($p< 0.05$) included age (B= -0.018; 95% CI: -0.024 to -0.013), education (B= 0.053; 95% CI: 0.037 to 0.068), sex (B= -0.171; 95% CI: -0.264 to -0.079), early life SES (B= 0.073; 95% CI: 0.012 to 0.134), and social activities (B= 0.081; 95% CI: 0.010 to 0.153). Younger age, higher education, female sex, higher early life SES, and more social activities were all significant predictors (**Table 15**). Interestingly, the impaired group had appreciably different results. The final model for the impaired group (n=97) resulted in a R_2 of 0.299 and an Adjusted R_2 of 0.269 ($F(4, 92)=9.82$; $p< 0.001$). Significant predictors ($p<.05$) included education (B= 0.063; 95% CI: 0.030 to 0.095), BMI (B= 0.026; 95% CI: 0.006 to 0.045), diet (B= 0.071; 95% CI: 0.023 to 0.118), and physical activity (B= 0.094; 95% CI: 0.034 to 0.154). Higher education, higher BMI, better diet adherence, and higher physical activity were all significant predictors in the impaired group (**Table 16**).

AIM 2 REGRESSION RESULTS

Multiple linear regression was performed to determine the predictive ability of each Health Score on global cognition at analytic baseline. Each model consisted of one Health Score and four

demographic covariates (i.e., age, education, sex, early life SES, diagnosis). All models were significantly predictive of global cognition ($p< 0.05$); age, education, sex, and diagnosis were also significant in each of the four models, but early life SES was non-significant and thus removed from the final models (see **Table 17**, **Table 18**, **Table 19**, & **Table 20**). HS1, HS2, and H4 were significant predictors in their respective models, however, HS3 (the Risk/Disease approach) was not a significant predictor in the HS3 model (β=.001; p=0.925). Subsequently, a Meng Test for model comparisons (Meng, Rosenthal, & Rubin, 1992) was performed to compare the Health Score regression models with one another to determine significant differences in the predictive ability of global cognition (**Table 21**). HS1 was significantly different from HS3 (z= 4.737; $p<.001$) but was not significantly different from HS2 (z= -1.572; $p= 0.116$) or HS4 (z= 1.283; $p=0.200$). HS2 was significantly different from HS3 (z= 6.036; $p< 0.001$) and HS4 (z= 4.900; $p< 0.001$). HS3 was significantly different from HS4 (z= -6.159; $p<0.001$).

Post Hoc Aim 2 Exploratory Results

Diagnosis was a significant predictor in all models so additional post-hoc analyses were performed looking at the NCI and the impaired groups separately. All models were significantly predictive of global cognition ($p< 0.05$), with age, education, sex, and early life SES significant in each of the four models (see **Table 22**, **Table 23**, **Table 24**, and **Table 25**). HS1, HS2, and H4 were significant predictors in their respective models; however, HS3 was not a significant predictor in the HS3 model (B=0.008; p=0.520). For the impaired group, all models were significantly predictive of global cognition ($p< 0.05$); however, the covariates were slightly different across models. Age and education were the covariates for the HS1, HS2, and HS4 models; sex was additionally included in the HS3 model (see **Table 26**, **Table 27**, **Table 28**, and

Table 29). HS2 was the only significant predictor in its model (B=0.042; *p*=0.039) while HS1 (B=0.026; *p*=0.573), HS3 (B=-0.034; *p*=0.278), and HS4 (B=0.022; *p*=0.177) were not significant.

An additional analysis was performed which involved re-coding HS1 to be consistent with a data-driven approach of significant predictors for the impaired group (i.e., diet, physical activity, and BMI instead of social activities). The model including the re-coded HS1 (i.e., HS1-Im) was significant ($p < 0.05$), again driven by the covariates, but HS1-Im was not a significant predictor (B=0.039; *p*=0.087; **Table 30**).

AIM 3 RESULTS

Overview

Of the 467 participants with lifestyle data at analytic baseline, 112 participants had longitudinal cognitive assessments which were included in the analysis for Aim 3 (i.e., three or more years; mean years ± SD; range: 3.72 ± 0.80; 3-6 years). Compared to the full sample, the subset of 112 participants had slightly younger participants (average age of 82 versus 83 years old), the same average years of education (15 years), higher percentage of females (77% versus 73%), a tighter SES range (3.52 versus 4.16), and slightly higher percentage of APOE ε4 carriers (21% versus 20%). Regarding diagnosis, there were 94 participants with NCI, 18 participants with MCI, and 0 participants with AD which corresponded with 84%, 16%, and 0%, respectively, whereas the full sample had 77% NCI, 20% MCI, and 3% AD. All risk factors were nearly the same between the subset of 112 and the full sample (i.e., subset versus full sample; alcohol consumption: 5.58 grams versus 6.02 grams; percent past/current smokers: 37.5% versus 38.5%; depression

symptoms: 0.78 versus 1.04; BMI: 26.41 versus 26.7). For Lifestyle Factors, the subset had slightly better MIND diet adherence (7.9 versus 7.6) and slightly more physical activity (3.0 versus 2.7) and social activities (2.70 versus 2.57), but the same sleep fragmentation (0.028 versus 0.03) and perceived stress (2.06 versus 2.07).

Given that HS2 demonstrated a slightly, though not statistically, larger R-squared value in Aim 2 results and larger range, HS2 was used for the Aim 3 analyses. The possible range for the analytic baseline HS2 was 6 to 20 points, however the actual scores did not span the full range (min value=6; max value=17; see **Table 5**). HS2 scores were divided into quartiles at analytic baseline and labeled as Unfavorable (first quartile; 6 to 11.1), Minimally Favorable (second quartile; 11.1 to 12.1), Moderately Favorable (third quartile; 12.1 to 13.1) and Favorable (fourth quartile; 13.1 to 17. **Table 31** provides average slopes and standard deviations for each analytic baseline HS category. Averaged HS2 scores ranged from 8.6 to 16 and were similarly categorized by quartile into Unfavorable (8 to 11.1), Minimally Favorable (11.1 to 12.18), Moderately Favorable (12.18 to 13.61), and Favorable (13.61 to 16). **Table 32** provides cognitive change score means and standard deviations for averaged HS for each category. A between subjects one-way analysis of covariance (ANCOVA) was performed, separately, for each cognitive domain (i.e., global cognition, verbal memory, processing speed, working memory) both at analytic baseline (**Table 33**) and using the Averaged Health Score (**Table 34**). Initial models included covariates (i.e., age, education, sex, early life SES, diagnosis) significant at $p< 0.15$ but covariates were excluded in the final model if not significant at $p< 0.05$.

Global Cognition

One participant with a slope greater than 6 standard deviations from the mean was excluded from the global cognition analyses since the inclusion of this score was found to influence the results. With the outlier excluded (n=111), the overall global cognition slope of the sample was negative (mean ± SD; range: -0.0381 ± .079; -0.2675 to 0.1404). All five covariates were removed from the final models as none were significant predictors. Using the analytic baseline Health Score, the ANOVA examining rate of cognitive change between the HS2 categories was significant ($F(3,107)=2.84$; $p=0.042$) with the following global cognition slopes: Unfavorable (mean slope ± SD; -0.049 ± 0.068), Minimally Favorable (-0.070 ± 0.071), Moderately Favorable (-0.029 ± 0.096), and Favorable (-0.013 ± 0.071; see Figure 2). There were no post hoc, pairwise, significant differences between the Health Score categories. Using the Averaged Health Score, the ANOVA was not significant ($F(3,107)=2.05$; $p=.111$) with the following global cognition slopes: Unfavorable (mean slope ± SD, -0.057 ± .081), Minimally Favorable (-0.049 ± 0.075), Moderately Favorable (-0.039 ± 0.079), and Favorable (-0.010 ± 0.077; see Figure 3). Both analyses were underpowered. Observed power was 0.666 with an effect size of d=0.277 and 0.513 with an effect size of d=0.230 for the analytic baseline and averaged analyses, respectively. A total of 147 subjects (37 additional cases) or 212 subjects (101 additional cases) would have been needed to achieve 80% power with the same effect size for each analysis, respectively.

Verbal Memory

The overall verbal memory slope of the sample was negative (mean ± SD; range: -0.046 ± 0.138; -0.502 to 0.257). All five covariates were removed from the final model as none were significant

predictors. Using the analytic baseline Health Score, the ANOVA examining rate of cognitive change between the HS2 categories was not significant (F(3,108)=2.36; *p*=.076) with the following verbal memory slopes: Unfavorable (mean slope ± SD; -0.078 ± 0.149), Minimally Favorable (-0.079 ± 0.144), Moderately Favorable (-0.043 ± 0.143), and Favorable (0.002 ± 0.111; see Figure 2). Using the Averaged Health Score, the ANOVA was not significant (F(3,108)=1.16; *p*=.327; see Table 34) with the following verbal memory slopes: Unfavorable (mean slope ± SD, -0.082 ± 0.152), Minimally Favorable (-0.045 ± 0.132), Moderately Favorable (-0.040 ± 0.131), and Favorable (-0.016 ± 0.135; see Figure 3). Both analyses were underpowered. Observed power was 0.578 with an effect size of d=0.249 and 0.306 with an effect size of d=0.172 for the analytic baseline and averaged analyses, respectively. A total of 184 subjects (72 additional cases) or 376 subjects (264 additional cases) would have been needed to achieve 80% power with the same effect size for each analysis, respectively.

Processing Speed

Two participants were excluded from the processing speed analyses. One participant had only two years of processing speed data and the other was excluded due to a slope greater than 9 standard deviations from sample mean which was found to influence the results. With those two participants excluded (n=109), the overall Processing Speed slope of the sample was negative (mean ± SD; range: -0.069 ± 0.114; -0.4724 to 0.1905). All five covariates were removed from the final model as none were significant predictors. Using the analytic baseline Health Score, the ANOVA examining rate of cognitive change between HS2 categories was not significant (F(3,105)=0.645; *p*=0.588) with the following Processing Speed slopes: Unfavorable (mean slope ± SD, -0.061 ± 0.122), Minimally Favorable (-0.091 ± 0.116), Moderately Favorable (-

0.049 ± 0.112), and Favorable (-0.077 ± 0.111; see Figure 2). Using the Averaged Health Score, the ANOVA was not significant (F(3,105)=1.44; *p*=.236) with the following Processing Speed slopes: Unfavorable (mean slope ± SD, -0.067 ± 0.133), Minimally Favorable (-0.103 ± 0.090), Moderately Favorable (-0.076 ± 0.135), and Favorable (-0.040 ± 0.092; see Figure 3). Both analyses were underpowered. Observed power was 0.181 with an effect size of d=0.137 and 0.371 with an effect size of d=0.201 for the analytic baseline and averaged analyses, respectively. A total of 588 subjects (479 additional cases) or 276 subjects (167 additional cases) would have been needed to achieve 80% power with the same effect size for each analysis, respectively.

Working Memory

One participant was excluded from the working memory analyses due to a slope greater than 6 standard deviations from sample mean which was found to influence the results. With the outlier excluded (n=111), the overall Working Memory slope of the sample was negative (mean ± SD; range: -0.036 ± 0.118; -0.3747 to 0.4614). Four of the five covariates were removed from the final model as these were not significant predictors. Age was a significant predictor of Working Memory at analytic baseline (*p*=0.004) and using the averaged Health Score (*p*=0.007) and remained in the models. Using the analytic baseline Health Score, the ANCOVA examining rate of cognitive change between HS2 categories was significant (F(4,106)=3.61; *p*=0.009); however, the Health Score categories was not a significant predictor (*p*=0.182) with the following Working Memory slopes: Unfavorable (mean slope ± SD, -0.036 ± 0.118), Minimally Favorable (-0.041 ± 0.141), Moderately Favorable (0.014 ± 0.123), and Favorable (0.019 ± 0.130; Figure 2). Using the Averaged Health Score, the ANCOVA was significant (F(4,106)=3.63; *p*=.008), however the

Health Score category was not a significant predictor (p=.175) with the following Working Memory slopes: Unfavorable (mean slope ± SD, -0.043 ± 0.114), Minimally Favorable (0.003 ± 0.120), Moderately Favorable (-0.032 ± 0.120), and Favorable (0.034 ± 0.151; Figure 3). When excluding the age covariate, both analyses were underpowered. Observed power was 0.438 with an effect size of d=0.228 and 0.542 with an effect size of d=0.212 for the analytic baseline and averaged analyses, respectively. A total of 216 subjects (105 additional cases) or 248 subjects (137 additional cases) would have been needed to achieve 80% power with the same effect size for each analysis, respectively.

CHAPTER 6: Discussion

This project aimed to better understand the relationship between lifestyle factors and cognitive aging. This was accomplished by 1) examining the ability of individual demographic, risk, and lifestyle variables to predict cognition; 2) creating Health Scores comprised of different combinations of lifestyle and risk factors and assessing the predictive ability of these scores on cognition; and 3) comparing the rate of cognitive change (decline) between varying degrees of health. Aim 1 showed that primarily demographic factors and diagnosis predicted cognition; however, social activities and diet were lifestyle factors found to be significant in some analyses. Aim 2 demonstrated that a Health Score incorporating healthy lifestyle factors better predicted cognition than a Health Score incorporating risk factors alone. From Aim 3, though the sample size was significantly reduced and the analysis was underpowered, there was a trend towards slower global cognitive decline in individuals with more favorable lifestyle behaviors, in a dose dependent manner. The below discussion provides further explanation of the results.

PREDICTORS OF COGNITION (AIM 1)

Of the fifteen predictors entered into each model, fewer lifestyle variables than expected demonstrated significant predictive ability. As evident, demographic factors and diagnosis were consistently predictive while only social activities (for global cognition and processing speed), diet (for working memory), and depression (for processing speed) emerged as non-demographic predictors. The importance of demographic factors was unsurprising given their well-established link to cognition and interestingly, the present sample had a notably older mean age (i.e., 83) compared to other lifestyle studies with participant mean ages in the 60s and 70s (Anastasiou et

al., 2018; Lourida et al., 2019; Shakersain et al., 2018; Spencer et al., 2005; Visser et al., 2019). Similar to the present study, previous studies also found weaker association between cognition and health-related factors than demographic factors. For example, the Asset and Health Dynamics of the Oldest-Old study, a study of American older adults with common health problems (i.e., high blood pressure, heart disease, diabetes, lung disease, and stroke) demonstrated that demographic variables most strongly predicted performance on all cognitive scores (e.g., immediate and delayed recall of word list, orientation questions, working memory, etc.) while health variables had significant betas, but with notably smaller weights (Zelinski & Gilewski, 2003). Moreover, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a community sample of non-demented older adults, also found larger beta weights for demographic factors compared to medical factors (e.g., diabetes) in a multivariate regression model (Rexroth et al., 2013).

Early life socioeconomic status was another demographic factor that was significantly predictive of cognition in the current study. This body of literature is much less developed than other demographic variables (e.g., age, education, sex); however, it is rapidly emerging given national priority on limiting health disparities and working towards health equity, especially among older (Carnethon, Kershaw, & Kandula, 2019; Hodes & Bernard, 2020). The results of the present study support prior findings in that early life SES was linked to late life cognition but not cognitive decline (Greenfield & Moorman, 2019). Greenfield et al. found early life SES predictive of verbal fluency, but not verbal memory, while the present study found early life SES predictive of working memory, but not verbal memory or processing speed. Similarly, the

present study found that though early life SES may be an important cognitive predictor cross-sectionally, it does not seem to have predictive ability for rate of cognitive decline.

Though less prominent than the demographic factors, lifestyle factors and risk factors were significantly predictive of cognition in the present study. Higher frequency of social activities was a significant predictor of better global cognition and faster processing speed in the full sample. These results partially replicate findings from a study of the same general MAP cohort but using study entry instead of analytic baseline. James and colleagues found increased social activities to be cross-sectionally associated with global cognition but not with verbal memory, processing speed, or working memory (James, Wilson, et al., 2011). Interestingly, there was a significant time by social activities interaction effect for all cognitive domains, suggesting that increased social activities were consistently associated with reduced cognitive decline (James, Wilson, et al., 2011). It is well known that individuals may become withdrawn as cognition worsens, so perhaps the social activities measure was capturing a consequence of decline and not actually predicting it. Though more work is certainly needed to understand the link between social activities, cognition, and cognitive decline, our findings are in line with prior work showing social interaction as an important factor for cognitive outcomes (Katz et al., 2016; Sauter et al., 2019).

In the present study, better diet adherence was a significant predictor cross-sectionally of working memory in the full sample, but not of verbal memory or global cognition as expected. The lack of association runs against many other studies using different cohorts that did see an association between MIND diet and/or Mediterranean diet and global cognition and verbal

memory (Anastasiou et al., 2018; Marseglia et al., 2018; McEvoy et al., 2017; Wesselman et al., 2020). Perhaps the reason for diet not having predictive ability cross-sectionally for verbal memory is that maybe diet becomes important as a predictor of decline, and the effect can only be seen across timepoints. Prior results seen in the same general Rush cohort support this hypothesis. They found higher MIND diet adherence predictive of slower cognitive decline in all cognitive domains (Morris et al., 2015). The authors did not report cross-sectional associations between MIND diet adherence and cognition. This may suggest that there were no significant cross-sectional associations, especially because many other Rush studies analyzing different lifestyle factors comment on both cross-sectional and longitudinal predictive ability (Buchman et al., 2012; James, Wilson, et al., 2011; Lim, Kowgier, et al., 2013; Turner et al., 2017). Though this is speculative, it would explain why the present study also did not find significant associations between diet and cognition cross-sectionally.

Interestingly, though not observed in the full sample, diet was a significant predictor of global cognition for the impaired group. Lifestyle factors appear to be important predictors for impaired individuals (i.e., MCI and AD) as better MIND diet adherence as well as more physical activity were predictive of better cognition. This suggests that though diet may not be predictive cross-sectionally in non-impaired individuals, it is an important variable to consider for those with cognitive impairment. Anastasiou and colleagues presented similar findings. They examined the independent effects of lifestyle factors, including Mediterranean diet adherence, physical activity, sleep, and instrumental activities of daily living (IADL), on cognition and found diet and physical activity as well as IADLs to be associated with a global cognition composite (Anastasiou et al., 2018). This finding was seen in the nondemented individuals, which included

about 12% MCI participants. However, when they removed the MCI participants, diet remained but physical activity was no longer a significant predictor (Anastasiou et al., 2018). This further corroborates the present study's results of physical activity not being predictive of cognition in cognitively normal individuals. The Anastasiou study also measured processing speed and found physical activity and IADLs to be predictive (Anastasiou et al., 2018) which was different from the present study's findings. In the full sample of the present study, social activities and depression were predictive of processing speed and for the impaired group only, alcohol, APOE status and sex were predictive of processing speed. Anastasiou et al. did not measure social activities, perceived stress, or working memory, and the present study did not have an IADL measure nor a cognitive composite for executive functioning, language, or visuospatial ability, making further comparisons between studies challenging. Other studies lacked cognitive data, but associated higher healthy diet adherence with reduced odds of cognitive decline, slowed rates of cognitive decline, reduced conversion to AD, and improvements in cognitive functioning (Hardman et al., 2016; Hosking et al., 2019). Curiously, healthy diet being associated with positive outcomes in impaired individuals is not what a study in Brazil found. Calil and colleagues found MIND diet adherence associated with cognition only in non-impaired individuals, and not in participants with MCI or AD; however, the authors hypothesized there may have been other social health determinants influencing the results (e.g., socioeconomic status; Calil, Brucki, Nitrini, & Yassuda, 2018).

A literature review of physical activity in impaired individuals supported a positive association between physical activity and reduced risk of impairment in people with MCI and AD, (Lautenschlager, Cox, & Kurz, 2010) though large, well designed clinical trials are needed to

better understand the impact of physical activity on cognition because the trials are few and show only modest or partial benefits (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013; Lautenschlager et al., 2010). Healthy diet in impaired individuals has been previously associated with improved cognitive functioning (Brandt et al., 2019; Krikorian et al., 2012) though additional well-controlled studies are need to further understand the impact of diet on cognition. The BMI result was in the unexpected direction (i.e., higher BMI was associated with better cognition); however, weight loss and frailty are known markers of dementia (Shatenstein et al., 2001). Correspondingly, some studies have shown an overweight BMI in the elderly years is associated with beneficial health outcomes; however, this is an inconsistent finding and there has yet to be determined an optimal BMI for old age (Garcia-Ptacek et al., 2014; Memel et al., 2016; Schmeidler et al., 2019). Considering all of these factors together further highlights the complex nature of lifestyle and brain health.

HEALTH SCORE COMPARISONS (AIM 2)

The use of some type of "risk score" or "health score" is common in the literature; however, there is no gold standard formula of factors as evidenced by the variety of compositions in previous studies (Anastasiou et al., 2018; Li et al., 2018; Lourida et al., 2019; Spencer et al., 2005). To our knowledge, no study has compared the predictive ability of one Health Score composition versus another on cognition. In the current study, we compared four Health Scores which were comprised of variables selected with different approaches. The first (HS1) was a data driven approach and used the significant predictors from Aim 1, which in the full sample was only social activities. The second (HS2) included the healthy lifestyle factors exclusively (i.e.,

diet, physical activities, sleep fragmentation, social activities, perceived stress) while the third (HS3) included risk factors exclusively (i.e., depression, smoking, alcohol, BMI, APOE status). The fourth (HS4) consisted of all healthy lifestyle factors as well as all risk factors. Each model, which included one Health Score along with age, education, sex, and diagnosis, was significantly predictive of cognition; however, the Health Score consisting of risk factors alone was not a significant predictor in its model. When these models were compared head-to-head, the Health Score incorporating only lifestyle factors was designated as the "best" prediction of global cognition due to the slightly higher R-squared value and the more comprehensive approach to health (i.e., HS2 incorporated five factors while HS1 incorporated only one factor). This was further supported when looking at the impaired group separately, as the Health Score incorporating exclusively lifestyle factors was the only Health Score predictive of cognition among impaired individuals. Even when compared with a data-driven approach tailored to the impaired group, the healthy-lifestyle-only Health Score remained the best predictor. Overall, there appears to be an added benefit of including a range of healthy lifestyle behaviors, above and beyond the most parsimonious data-driven approach, for understanding how lifestyle factors relate to cognition, especially for the impaired group.

Though there was no Health Score comparison involved in their study, Anastasiou and colleagues came to a similar conclusion. Their Total Lifestyle Index score, comprised of diet, physical activity, sleep and instrumental activities of daily living, was significantly predictive of almost all cognitive domains (i.e., memory, executive functioning, visuospatial, attention/speed, and language; Anastasiou et al., 2018). Conversely, when the variables were examined independently, each lifestyle factor was significantly related to a few domains and had non-

significant but trending associations with other domains (Anastasiou et al., 2018). Their study, along with the present study, provides support that individual lifestyle factors may have weak or even non-significant associations with various cognitive domains that cannot be routinely detected independently, but may have a cumulative effect when examined in concert.

Although many composite health scores focus on or include unhealthy behaviors, this was not the focus of the present study or the Anastasiou et al. study. However, the present study did include a Health Score comprised of unhealthy behaviors (e.g., alcohol, smoking, and BMI) which was not predictive of cognition. Further research is needed to tease apart the different predictive abilities of healthy behaviors versus unhealthy behaviors on cognition, and focusing on healthy lifestyle behavior may be advantageous.

HEALTH SCORE CATEGORIES (AIM 3)

When the cognitive slopes were compared across the four health categories (Unfavorable, Minimally Favorable, Moderately Favorable, Favorable), the more favorable Health Scores were associated with reduced rate of cognitive decline in a mostly dose-dependent manner, though all analyses were underpowered. Global cognition was the only significant result; however, verbal memory was trending in the predicted direction. This suggests that individuals with higher Health Scores, used in this study as a proxy for overall health, have a slower rate of global cognitive decline compared to individuals with a less favorable Health Score. This is consistent with prior research using Health Scores to predict cognitive decline. For example, in a cohort of Dutch older adults, a healthy Lifestyle Score based on smoking status, alcohol consumption, physical activity, and BMI was predictive of a slower decline in MMSE scores, a common

measure of global cognition, than individuals with unhealthy Lifestyle Scores (Visser et al., 2019). Similarly, Shakersain et al. reported a slower decline in MMSE score in a group of dementia free older adults with an active lifestyle, consisting of healthy diet and participation in physical, social, and mental activities, compared to those with an inactive lifestyle (Shakersain et al., 2018). The present study utilized more robust cognitive data than the MMSE and extends the literature by showing a similar effect, namely that a healthy lifestyle is associated with slowed global cognitive decline compared to an unhealthy lifestyle.

It was unexpected that the other cognitive domains (i.e., processing speed and working memory) showed such variability in rate of cognitive change. These findings may be the result of an underpowered analysis, or it could be that health score categories do not sufficiently predict cognitive change in these domains. It is possible that other, non-lifestyle factors, or demographic factors may be important for understanding cognitive changes in these domains. For example, vascular factors not assessed in this study could impact processing speed and working memory performance. Further studies are needed to understand the relationship between Health Scores and rate of cognitive change in each cognitive domain.

CHANGING THE NARRATIVE: A FOCUS ON HEALTH NOT DISEASE

In this study, healthy lifestyle behaviors provided more information about cognition and cognitive decline in individuals with and without cognitive impairment than focusing on unhealthy lifestyle factors. This shift in perspective towards healthy lifestyle behavior is in line with what Diehl and colleagues call for in a galvanizing publication about changing the narrative

of aging (Diehl, Smyer, & Mehrotra, 2020). Diehl et al. acknowledged that though individuals may be susceptible to hereditary ailments or environmental factors, age-related changes can be influenced through behavior and lifestyle modifications (Diehl et al., 2020). He proposed that "middle-aged and older adults have the opportunity … to take control of their own aging." Many of the well-known healthy behaviors discussed in the literature review, including becoming physically active, eating a healthy diet, participating in cognitively stimulating activities, and abstaining from smoking, have been liked to cognitive outcomes. Changing the aging conversation from loss and decline to opportunity and challenge allows new narratives and beliefs about aging to emerge, which may in turn alter behavior, slow the rate of cognitive decline, delay or avoid the onset of dementia, and reduce financial and caregiving burdens worldwide.

Changing the narrative has been and will continue to be a challenging task; however, it is a needed step in realizing behavioral changes. Negative biases towards aging develop early in life and can turn into self-fulfilling prophesies when older individuals believe there is nothing to be done about their aging process (Diehl et al., 2020). Many individuals have limited knowledge of risk factors, causes, and prevention strategies of cognitive disorders such that their focus is disproportionally on family history (Rosenberg, Coley, et al., 2020) which can limit their belief in and openness to primary prevention strategies.

Working toward a new narrative is also difficult in the context of a disease-focused health care model. The U.S. has been criticized for having "sick care" instead of health care with financial incentives to perform procedures and prescribe medication instead of behavioral interventions

(Fani Marvasti & Stafford, 2012). The biomedical model defines health as the absence of disease; however, with chronic diseases being the primary problem, lifestyle changes are too often overlooked. The biomedical model sets the expectation that treatment is something that is done to or performed on a patient and requires a medical professional to achieve; however, many lifestyle changes can be self-directed. Additionally, this model largely ignores subclinical changes, which is often the time for behavioral interventions, especially in conditions with insidious onset like Alzheimer's disease.

The conventional health care system is already changing. Fee-for-service models are being replaced with outcomes-based reimbursements which may provide the ideal environment for a new narrative to be adopted. New narratives are taking shape in other areas of health care as well. There has been substantial progress made redefining health disparities and moving towards health equity (Carnethon et al., 2019) based on research highlighting social determinants of health (e.g., poverty, lack of access to quality education or employment, unhealthy housing, unfavorable work, neighborhood conditions, etc.; Braveman, Egerter, & Williams, 2011). These factors are particularly relevant for the design and implementation of behavior modifications to promote health. Under the new narrative and new health care model, individuals and communities would be more empowered to take control of their health and more resources would be routed to prevention. Given there is no effective treatment for Alzheimer's disease and the literature suggests that healthy lifestyle behaviors afford more favorable cognitive outcomes, it would be prudent to prioritize prevention efforts. These could be at a systemic level (e.g., improving conditions in low-income housing, implementing strategies for better health education, eliminating environmental hazards, and improving the diversity and cultural

sensitivity of health systems) or an individual level (e.g., health coaches, individualized diet plans, customized exercise protocol, social connectedness assessment, etc.). There are innumerable possible directions, but large, well-controlled prevention trials will be essential in this process.

LIMITATIONS

There are several limitations with this study that warrant mention, including aspects related to participant selection, variable measurement, and analyses performed.

Participant selection

The sample of individuals with all five lifestyle variables was relatively limited (i.e., n=476 out of a possible n=2,134 enrolled in the Memory and Aging Project) and decreased further when requiring three or more time points (n=112). This resulted in some analyses being underpowered (i.e., Aim 3). An analytic baseline timepoint was used to optimize the sample for participants with all five lifestyle variables; however, this left several years of partial data unexamined and the number of participants designated as MCI quite small. Had the sample been larger, there may have been higher numbers in the MCI group improving comparison between nonimpaired and impaired groups and allowing examination of predictors of cognitive diagnosis.

The present study had a relatively low incidence of depression symptoms, current smokers, and moderate to heavy alcohol users. A cohort with more risk factors could have provided greater differentiation between the Favorable and Unfavorable groups revealing further cognitive

benefits with healthy lifestyle behaviors. However, it is also possible that the opposite would have resulted. The sample was 95% Caucasian, limiting the generalizability of these findings to diverse groups. Future studies should be larger and incorporate participants with more variable lifestyles at baseline and greater racial and sociocultural diversity.

Variable measurement

There are some limitations in how variables were measured. First, physical activity was measured via an actigraph, which affords many benefits compared to subjective measures of activity, but does not measure intensity of activity. Descriptive information about the type and intensity of activity would provide richer data and opportunities for targeted intervention recommendations. Second, the MIND diet score was an adherence score based on how much a participant's diet overlapped with the designated dietary elements; the participants were not explicitly following the MIND diet. Third, the perceived stress measure was collected annually but queries stress during the past month. A discrepancy may have resulted in overreporting acute stress and underreporting chronic stress, which together muddies the overall perceived stress variable. Additionally, some lifestyle measures (i.e., diet, social activities, perceived stress) relied on self-report which may have been prone to misremembering and thus inaccurate data collection, as greater than 20% of the analytic baseline sample had MCI or AD. Regarding the risk factors, there are many other medical risk factors that were not examined in the present study (e.g., hypertension, diabetes, etc.) and incorporating such factors may have changed the results.

Two additional factor that likely influenced the results of this study was the point allocation process of deriving Health Scores, especially the risk factor variables, and assumptions about the cognitive slope. Unlike the lifestyle factors, the risk factors points were allocated based on *a priori* designations instead of quartiles. The Health Score consisting of risk factors alone (i.e., HS3) consistently lacked predictive ability of cognition in the analyses which could have been due to how points were allocated to the individual factors. When determining point allocation, decisions were made as to what constituted "healthier," and it is possible that if those decisions were different, there would be different results. For example, "healthy weight" was allocated the most points and based on standard BMI guidelines; however, few studies suggest "overweight" BMI (BMI > 25) is protective from cognitive decline in older adults (Garcia-Ptacek et al., 2014; Memel et al., 2016). Similarly, most studies agree that heavy alcohol consumption is not healthy but there is disagreement about the benefits of abstinence versus moderate alcohol consumption. Greater consistency in how studies define healthy lifestyle behaviors would help clarify the role of these factors. Regarding the cognitive slope, it is well known that the rate of cognitive decline can be variable. At times, cognitive decline can occur slowly whereas at other times it can occur rapidly. For the present study, the slope was modeled linearly and variably in the rate of decline was not accounted for. It is possible that a nuanced model could have captured more accurate rates of cognitive decline and subsequently led to different findings.

FUTURE DIRECTIONS

Many of these limitations present opportunities for future studies exploring the relationship between cognition and lifestyle factors. Practical and specific recommendations for future research based on the present study would be to include a physical activity measure from which

activity intensity can be obtained, to consider adherence scores of individuals who follow the MIND diet, and to incorporate a perceived stress measure with a wider scale. Regarding outcomes, the present study used cognition as the primary outcome, but future analyses could conduct survival analyses, specifically proportional hazards models, to assess the impact of lifestyle factors on risk of progressing from non-impaired to MCI or MCI to AD. It would also be interesting to incorporate healthy lifestyle factors into well-established risk models (e.g. Framingham risk score) to determine if healthy behaviors have additive predictive ability. In addition, latent profile analysis could be used to identify patterns among health behaviors that predict cognition or diagnosis, rather than pre-determined Health Scores, as seen in prior studies (e.g., Mawditt et al., 2016; Norton et al., 2012).

Lastly, future directions must include the implementation of behavioral interventions in multiple domains, which should address social determinants of health of the study participants and incorporate education for patients, practitioners, and communities. For patients, multi-domain lifestyle interventions are ongoing worldwide (Rosenberg, Mangialasche, Ngandu, Solomon, & Kivipelto, 2020), and a recent study presented promising results for both face-to-face and digitally mediated interventions to enhance cognitive reserve and reduce risk of Alzheimer's disease (Bott et al., 2019). For practitioners, professional organizations, such as the American College of Lifestyle Medicine or the American College of Preventive Medicine, could help educate and provide additional training to health care workers on assessment and implementation of healthy lifestyle behaviors in their patients. Additionally, conversations about healthy lifestyle behaviors could be incorporated into the medical school curricula ensuring the next generation of doctors are provided this information. For communities, psychoeducation and correcting

preconceived notions about dementia may facilitate implementation of evidenced-based strategies (Maust et al., 2019), especially when using results from community-intervention pilot programs to guide and bolster implementation (e.g., Sims-Gould, Franke, Lusina-Furst, & McKay, 2020). There are already ongoing initiatives (e.g., Reframing Aging Initiative), though more are needed.

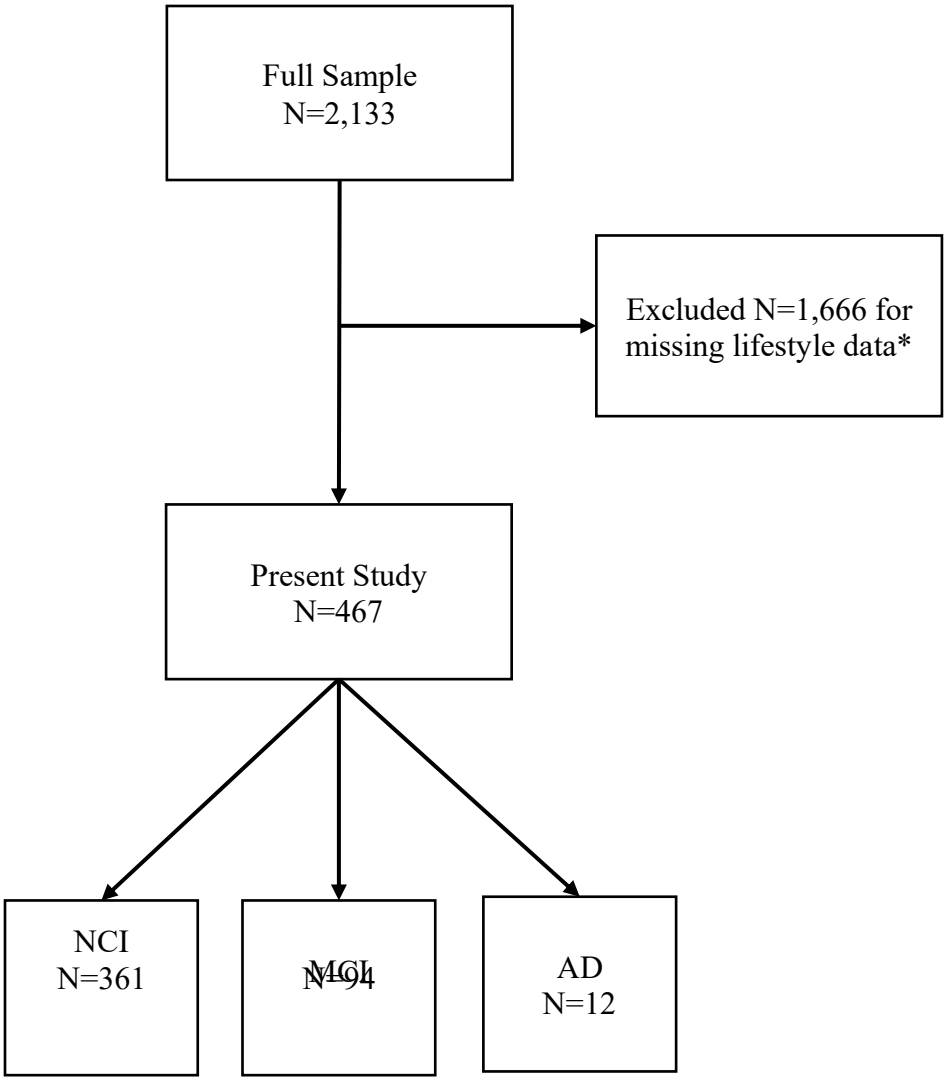
SUMMARY AND CONCLUSION

In conclusion, this study examined the effects of lifestyle factors on cognition in aging adults and found that overall, healthy lifestyle behaviors were predictive of cognition, especially for individuals who already had cognitive impairment. Additionally, a composite Health Score derived from only healthy lifestyle behaviors was the best predictor of cognition compared to Health Scores that focused either only on risk factors or a combination of risk and healthy lifestyle factors. This was a novel finding and to our knowledge no prior study has compared Health Scores formed from different types of variables. Lastly, the rate of global cognitive decline was slower in individuals with more favorable Health Scores, in a mostly dose dependent manner. These results provide evidence that healthy lifestyle behaviors predict cognition better than risk behaviors and encourages further exploration of the additive impact of multiple healthy behaviors on cognitive outcomes, particularly within the context of aging and Alzheimer's disease.

FIGURES

Figure 1

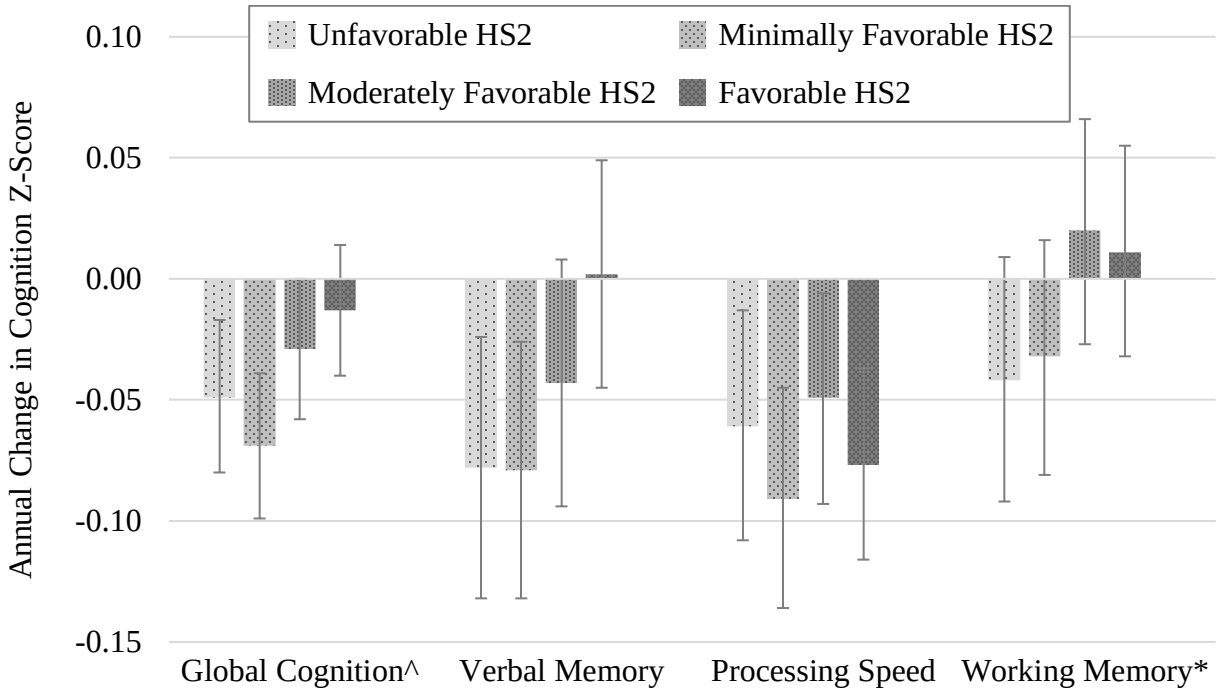
Sample Breakdown with Exclusion Criteria



Note. NCI= no cognitive impairment; MCI= mild cognitive impairment;
AD= Alzheimer's dementia.
*Any participant missing one or more lifestyle variables (i.e., diet, physical activity, sleep fragmentation, social activities, or perceived stress) was excluded.

Figure 2

Rate of Cognitive Change by Analytic Baseline Health Score Category for Each Cognitive Domain



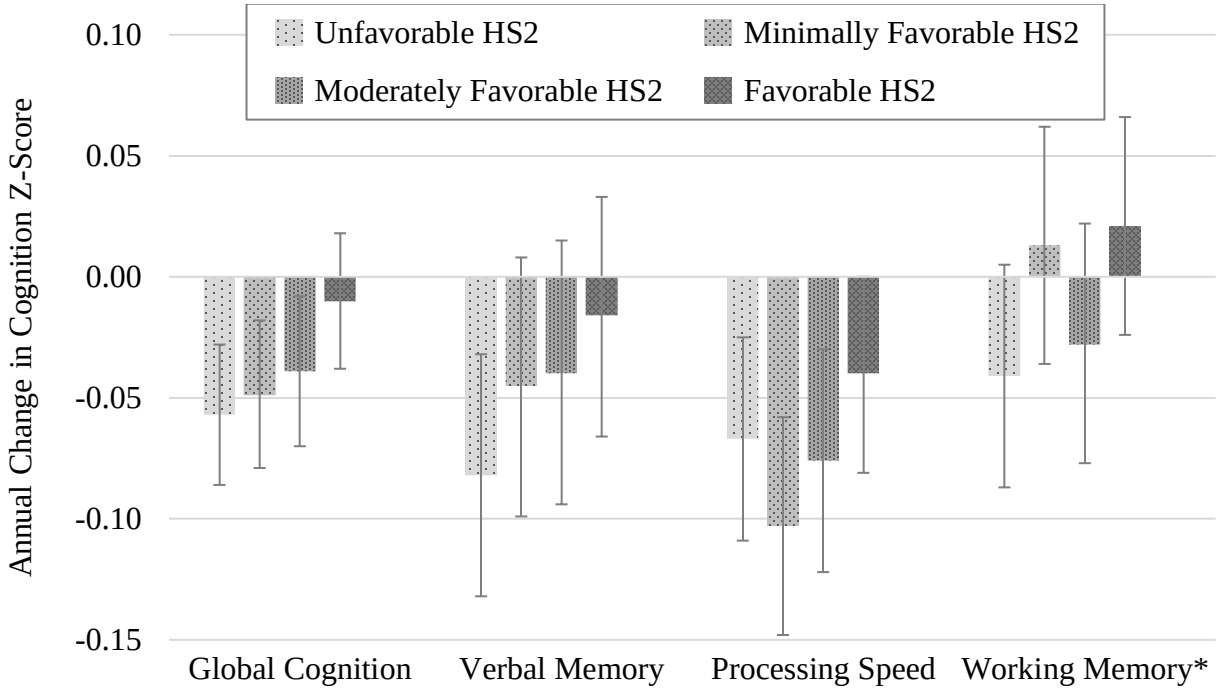
Note. HS = Health Score. Health Scores presented are HS2 scores. HS2 includes diet, physical activity, sleep fragmentation, social activities, and perceived stress. Error Bars represent 95% confidence intervals.

^The Global Cognition model was significant, but there were no significant differences between the health score categories. The Verbal Memory and Processing Speed models were not significant.

* The Working Memory model controls for age which caused the overall model to be significant, but there were no differences between health score categories.

Figure 3

Rate of Cognitive Change by Averaged Health Score Category for Each Cognitive Domain



Note. HS = Health Score. Health Scores presented are HS2 scores. HS2 includes diet, physical activity, sleep fragmentation, social activities, and perceived stress. Error Bars represent 95% confidence intervals. There were no significant differences between health score categories for any of the cognitive domains.

* The Working Memory model controls for age which caused the overall model to be significant, but there were no differences between health score categories.

TABLES

Table 1

Diets

Diet Name	Reference	Details
Mediterranean	Serra-Majem et al., 2006 Mastorakou et al., 2019	Minimally processed, seasonally fresh, and locally grown; emphasizes plant foods and olive oil with low to moderate amounts of dairy and wine. Infrequent red meat and egg consumption; desserts made of fresh fruits, nuts and olive oil
DASH	Appel et al., 2006 Services, 2006	Low sodium; low fat; limit red meat and sugar; eat whole grains, fruits/vegetables, fish, poultry, nuts
MIND	Morris et al., 2015	Eat: green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil and wine Limit: red meats, butter, stick margarine, cheese, pastries, sweets, fried/fast food
Adkins/ketogenic	Peterman, 1925	High fat, low protein and carbohydrates

Note. DASH = Dietary Approach to Stop Hypertension; MIND = Mediterranean-DASH

Intervention for Neurological Delay

Table 2

Prior Health Score Methodologies

Type	Method	Examples
Lifestyle Index (Anastasiou et al., 2018)	Combines multiple factors together into one number to derive a Health Score	Total Lifestyle Index= sum score (range 0-12; higher values indicating an overall beneficial lifestyle) of rating 0-4 depending on quartile for diet, physical activity, sleep, and ADL functioning.
Lifestyle Score (Spencer et al., 2005)	Combines multiple factors together into one number to derive a Health Score	Lifestyle Score= sum score (range 0-8) of "prudent" lifestyle behaviors: 1-having either never smoked or having stopped smoking more than 1 year previously; 2-doing a minimum of 3 hours of at least moderate physical activity weekly; 3- having no more than two alcoholic drinks daily; 4-eating fish at least three times weekly; 5-eating meat less than five times weekly; 6-never adding salt to food; 7-having a self-reported body mass index (BMI) of 25.0 kg/m2 or less; 8-using reduced fat or skim milk
Lifestyle Risk Score (Li et al., 2018)	Combines multiple factors together into one number to derive a Risk Score	Lifestyle Risk Score= sum score (range 0-5) of diet, smoking, physical activity, alcohol consumption, and BMI. A score of 1 was given if the factor was low risk and a 0 if it was high risk. The range was 0-5 with high scores representing lower risk lifestyle.
Lifestyle Score into 3 Categories (Lourida et al., 2019).	Combines multiple factors together into a Health Score then Health score is divided into categories	Lifestyle Index Score=sum score (range 0-4; higher scores indicating higher adherence to healthy lifestyle) of 1-no current smoking, 2-regular physical activity, 3-healthy diet, and 4-moderate alcohol consumption; one point per healthy lifestyle behavior was granted. Scores were then separated into 3 categories to compare against each other: Favorable (3-4 healthy factors) vs Intermediate (2 healthy factors) vs Unfavorable (0 or 1 healthy factor).

Two factors-observational (Shakersain et al., 2018)	Factors are looked at independently and then combined	Diet was "tertiled" into Low, Moderate, or High adherence based on diet index score. Participation in physical, mental and social activities was trichotomised into Low, Moderate, and Intense. The study examined the effects of diet on cognition, activity on cognition, and both diet and activity on cognition using mixed effects models with multiple imputation by chained Equation for missing data.
Two factors (Scarmeas et al., 2009)	Factors are looked at independently and then combined	Mediterranean Diet was trichotomized (low, middle, or high) and dichotomized (low or high). Physical activity (sum of weekly participation in activities, weighted by the intensity [light, moderate, vigorous] was trichotomized (no physical activity, some, or much) and dichotomized (low or high). Low diet + no physical activity group compared to High diet + much physical activity.
Two factors-interventional (Blumenthal et al., 2019)	Intervention study-2x2 factorial design	Participants were randomized into 4 groups (exercise alone, DASH diet alone, combo of exercise and DASH, or health education). Cognition was measures before and after the 6-month intervention and groups were compared.

Table 3

Neuropsychological Assessment Measures by Domain

Cognitive Domain	Tests
Verbal Memory (7 measures)	Immediate Recall Logical Memory Story A Delayed Recall Logical Memory Story A Immediate Recall East Boston Story Delay Recall East Boston Story Word List Memory Word List Recall Word List Recognition
Semantic Memory (3 measures)	15-item Boston Naming Test Verbal Fluency (Categories: Animals & Fruits/Vegetables) 15-item Reading Test
Working Memory (3 measures)	Digit Span Forwards Digit Span Backwards Digit Span Ordering
Processing Speed (4 measures)	Symbol Digit Modalities Test Number Comparison Stroop Word Reading Stroop Color Naming
Visuospatial Ability (2 measures)	15-item Judgment of Line Orientation 16-item Standard Progressive Matrices
Global Cognition (19 measures)	All of the above

Note. Verbal Memory and Processing Speed were referred to as Episodic Memory and Perceptual Speed in the prior Rush studies.

Table 4

Health Score Ratings

Variable (range of scores)	**1 point**	**2 points**	**3 points**	**4 points**
Diet (0-15)§	1st quartile	2nd quartile	3rd quartile	4th quartile
Physical Activity§	1st quartile	2nd quartile	3rd quartile	4th quartile
Sleep Fragmentation§	4th quartile	3rd quartile	2nd quartile	1st quartile
Social Activities (0-5)†§	1st quartile	2nd quartile	3rd quartile	4th quartile
Perceived Stress (0-4)§	3-4	2-2.9	1-1.9	0-0.9
Depression Score (0-10)^	7-10	4-6	1-3	0
Alcohol (amount)^	>2 drinks/day	1-2 drinks/day	< 1 drink/day	None
Smoking (status)^	Current		Past	Never
APOE genotype^	44	24, 34	33	22, 23
BMI*^	35 +	30 to 34.9	<18.5 & 25 to 29.9	18.5-24.9

Note. *BMI of 35+ corresponds with Class 2 & 3 Obesity; 30 to 34.9 corresponds with Class 1 Obesity; <18.5 corresponds with Underweight; 25 to 29.9 corresponds with Overweight; 18.5 to 24.9 correspond with Healthy Weight.

†= variables included in HS1

§= variables included in HS2

^ = variables included in HS3

All variables are included in HS4

Table 5

Health Score Characteristics

	HS1	HS2	HS3	HS4
Components	Social Activities	Diet Physical Activity Sleep Frag Social Activities Perceived Stress	Alcohol Use Depression Smoking APOE ε4 BMI	Diet Physical Activity Sleep Frag Social Activities Perceived Stress Alcohol Use Depression Smoking APOE ε4 BMI
Approach	Scientific	Lifestyle/Health	Risk/Disease	Comprehensive
Mean	2.4	12.1	16.5	28.7
Median	3	12	17	29
SD	1.1	2.5	1.7	3.1
Range	1 to 4	6 to 19	10 to 20	19 to 36

Note. n=467 for HS1 and HS2; n=451 for HS3 and HS4 due to missing BMI data (n=16).

SD = standard deviation. Data displayed is from the Analytic Baseline Health Scores.

Table 6

Sample Characteristics

	Descriptive Statistics				
	Mean	SD	n (%)	Median	Range
Demographic Factors					
Analytic Baseline Year	4.52	2.28		4.0	1 – 14
Age	83.40	7.10		84.5	61 – 100*
Education	15.00	2.70		15.0	7 – 20
Sex (female)			342 (73)		
Early Life SES	0.001	0.70		-0.004	-2.35 – 1.81
Race (white)			442 (95)		
APOE ε4 (≥ 1 copy)			95 (20)		
Risk Factors					
Depression Sx	1.04	1.63		0	0 – 9
Alcohol in grams	6.02	13.60		0	0 – 100.2
Smoking (past & current)			180 (38.5)		
BMI	26.70	5.20		25.8	14.3 – 52.7
Lifestyle Factors					
Diet	7.60	1.90		7.5	2 – 13
Physical Activity	2.70	1.50		2.5	0.2 – 10.5
Sleep Frag.	0.03	0.01		0.03	0.02 – 0.07
Social Activities	2.57	0.60		2.67	1.0 – 4.5
Perceived Stress	2.07	0.46		2.0	0.25 – 3.25
Cognition Z-Scores					
Global Cognition (n=467)	0.130	0.56		0.18	-2.2 – 1.5
Verbal Memory (n=466)	0.252	0.73		0.31	-2.5 – 1.8
Processing Speed (n=459)	0.030	0.79		0.07	-2.2 – 2.6
Working Memory (n=467)	-0.002	0.73		-0.04	-1.8 – 2.0
Diagnosis at Analytic Baseline					
Not Cognitively Impaired			361 (77)		
Mild Cognitive Impairment			94 (20)		
Alzheimer's Disease			12 (3)		

Note. * Frequency of age by decade are as follows: n=22 (60s), 109 (70s), 265 (80s), 70 (90s), 1 (100s); SD = standard deviation; SES = socioeconomic status; APOE = Apolipoprotein E; BMI = body mass index; sleep frag = sleep fragmentation.

Table 7

Multiple Linear Regression Predicting Global Cognition with Significant Demographics, Risk Factors, and Lifestyle Factors—Initial Model

					95 % CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.018	0.003	-0.230	< **0.001**	-0.024	-0.012
Education	0.055	0.007	0.275	< **0.001**	0.040	0.069
Sex (male)	-0.181	0.044	-0.146	< **0.001**	-0.267	-0.095
Early Life SES	0.051	0.028	0.066	*0.069*	-0.004	0.105
Diagnosis	-0.525	0.042	-0.452	< **0.001**	-0.607	-0.443
APOE ε4	-0.091	0.045	-0.068	**0.045**	-0.180	-0.002
Depression Sx	-0.004	0.012	-0.011	0.755	-0.028	0.020
Alcohol	0.001	0.001	0.021	0.550	-0.002	0.004
Smoking	0.032	0.040	0.028	0.423	-0.046	0.110
BMI	0.001	0.004	0.007	0.850	-0.007	0.008
Diet	0.016	0.010	0.056	*0.115*	-0.004	0.037
Physical Activity	0.008	0.013	0.021	0.559	-0.018	0.033
Sleep Frag.	-1.870	3.063	-0.021	0.542	-7.889	4.150
Social Activities	0.066	0.033	0.071	**0.048**	0.001	0.131
Perceived Stress	-0.008	0.040	-0.007	0.840	-0.087	0.071
$R_2 = 0.534$; $R_{2Adj} = 0.518$; $F(15, 430)=32.92$; $p < 0.001$						

Note. Values in **bold** are significant at $p< 0.05$. Values in *italics* are significant at $p< 0.20$. Diagnosis is coded with higher values indicating more impairment. SES = socioeconomic status; APOE = Apolipoprotein E; Depression Sx = depression symptoms; BMI = body mass index; Sleep Frag = sleep fragmentation. N=446.

Table 8

Multiple Linear Regression Predicting Global Cognition with Significant Demographics, Risk Factors, and Lifestyle Factors—Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.019	0.003	-0.235	< 0.001	-0.024	-0.013
Education	0.060	0.007	0.293	< 0.001	0.047	0.073
Sex (male)	-0.152	0.041	-0.120	< 0.001	-0.231	-0.072
Social Activities	0.077	0.032	0.082	0.015	0.015	0.139
Diagnosis	-0.580	0.038	-0.507	< 0.001	-0.655	-0.505
$R_2 = 0.542$; $R_{2Adj} = 0.537$; $F(5, 461) = 109.15$; $p < 0.001$						

Note. Diagnosis is coded with higher values indicating more impairment. N=462.

Table 9

Multiple Linear Regression Predicting Verbal Memory with Significant Demographics, Risk Factors, and Lifestyle Factors—Initial Model

					95 % CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.019	0.004	-0.184	< **0.001**	-0.027	-0.010
Education	0.059	0.010	0.228	< **0.001**	0.039	0.079
Sex (male)	-0.315	0.061	-0.195	< **0.001**	-0.434	-0.195
Early Life SES	-0.019	0.038	-0.019	0.628	-0.094	0.057
Diagnosis	-0.753	0.058	-0.500	< **0.001**	-0.866	-0.639
APOE ε4	-0.116	0.063	-0.067	*0.065*	-0.239	0.007
Depression Sx	0.016	0.017	0.035	0.346	-0.017	0.049
Alcohol	0.000	0.002	0.005	0.898	-0.003	0.004
Smoking	0.043	0.055	0.029	0.438	-0.065	0.150
BMI	0.001	0.005	0.010	0.797	-0.009	0.011
Diet	0.014	0.014	0.036	0.337	-0.014	0.042
Physical Activity	0.015	0.018	0.032	0.395	-0.020	0.051
Sleep Frag.	-1.842	4.249	-0.016	0.665	-10.194	6.509
Social Activities	0.008	0.046	0.006	0.866	-0.083	0.098
Perceived Stress	-0.071	0.055	-0.046	*0.199*	-0.180	0.038
$R_2 = 0.471$; $R_{2Adj} = 0.452$; $F(15, 429) = 25.44$; $p < 0.001$						

Note. Values in **bold** are significant at $p < 0.05$. Values in *italics* are significant at $p < 0.20$. Diagnosis is coded with higher values indicating more impairment. SES = socioeconomic status; APOE = Apolipoprotein E; Depression Sx = depression symptoms; BMI = body mass index; Sleep Frag = sleep fragmentation. N=445.

Table 10

Multiple Linear Regression Predicting Verbal Memory with Significant Demographics, Risk Factors, and Lifestyle Factors—Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.019	0.004	-0.181	< 0.001	-0.026	-0.012
Education	0.055	0.009	0.207	< 0.001	0.037	0.072
Sex (male)	-0.297	0.056	-0.181	< 0.001	-0.407	-0.186
Diagnosis	-0.801	0.051	-0.542	< 0.001	-0.902	-0.700
$R_2 = 0.478$; $R_{2Adj} = 0.473$; $F(4, 461) = 105.46$; $p < 0.001$						

Note. Diagnosis is coded with higher values indicating more impairment. N=466.

Table 11

Multiple Linear Regression Predicting Processing Speed with Significant Demographics, Risk Factors, and Lifestyle Factors—Initial Model

					95 % CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.031	0.005	-0.275	**< 0.001**	-0.041	-0.021
Education	0.043	0.013	0.148	**0.001**	0.017	0.068
Sex (male)	-0.212	0.076	-0.118	**0.006**	-0.362	-0.062
Early Life SES	0.025	0.048	0.022	0.603	-0.070	0.120
Diagnosis	-0.438	0.073	-0.259	**< 0.001**	-0.580	-0.295
APOE ε4	-0.150	0.079	-0.077	*0.058*	-0.305	0.005
Depression Sx	-0.042	0.021	-0.082	**0.046**	-0.084	-0.001
Alcohol	0.001	0.002	0.026	0.533	-0.003	0.006
Smoking	0.045	0.069	0.028	0.509	-0.090	0.181
BMI	-0.002	0.006	-0.010	0.807	-0.014	0.011
Diet	0.002	0.018	0.006	0.895	-0.033	0.038
Physical Activity	0.026	0.023	0.049	0.252	-0.019	0.070
Sleep Frag.	-9.263	5.324	-0.072	*0.083*	-19.727	1.201
Social Activities	0.163	0.058	0.121	**0.005**	0.049	0.277
Perceived Stress	0.076	0.069	0.044	0.274	-0.060	0.212
$R_2 = 0.341$; $R_{2Adj} = 0.317$; $F(15, 425)=14.65$; $p < 0.001$						

Note. Values in **bold** are significant at $p< 0.05$. Values in *italics* are significant at $p< 0.20$. Diagnosis is coded with higher values indicating more impairment. SES = socioeconomic status; APOE = Apolipoprotein E; Depression Sx = depression symptoms; BMI = body mass index; Sleep Frag = sleep fragmentation. N=441.

Table 12

Multiple Linear Regression Predicting Processing Speed with Significant Demographics, Risk Factors, and Lifestyle Factors—Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.031	0.005	-0.275	< 0.001	-0.040	-0.022
Education	0.045	0.011	0.155	< 0.001	0.023	0.067
Sex (male)	-0.206	0.070	-0.115	0.003	-0.343	-0.069
Depression Sx	-0.046	0.019	-0.095	0.016	-0.084	-0.009
Social Activities	0.168	0.054	0.127	0.002	0.061	0.275
Diagnosis	-0.488	0.067	-0.297	< 0.001	-0.619	-0.357
R_2 = .339; R_{2Adj} = .330; $F(6, 452)$= 38.56; p< 0.001						

Note. Diagnosis is coded with higher values indicating more impairment. Depression Sx = depression symptoms. N=459.

Table 13

Multiple Linear Regression Predicting Working Memory with Significant Demographics, Risk Factors, and Lifestyle Factors—Initial Model

					95 % CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.005	0.005	-0.049	0.343	-0.015	0.005
Education	0.042	0.013	0.160	**0.001**	0.017	0.068
Sex (male)	-0.106	0.077	-0.064	*0.172*	-0.257	0.046
Early Life SES	0.116	0.049	0.114	**0.018**	0.020	0.212
Diagnosis	-0.368	0.073	-0.238	**< 0.001**	-0.512	-0.223
APOE ε4	-0.026	0.080	-0.014	0.748	-0.183	0.131
Depression Sx	-0.003	0.022	-0.007	0.877	-0.046	0.039
Alcohol	0.004	0.002	0.067	*0.145*	-0.001	0.008
Smoking	-0.027	0.070	-0.018	0.697	-0.165	0.110
BMI	0.005	0.007	0.038	0.422	-0.008	0.018
Diet	0.033	0.018	0.084	*0.077*	-0.004	0.069
Physical Activity	-0.017	0.023	-0.036	0.452	-0.062	0.028
Sleep Frag.	3.295	5.397	0.028	0.542	-7.313	13.902
Social Activities	0.079	0.059	0.064	*0.177*	-0.036	0.194
Perceived Stress	0.020	0.071	0.012	0.782	-0.119	0.158
$R_2 = 0.180$; $R_{2Adj} = 0.151$; $F(15, 430)=6.28$; $p< 0.001$						

Note. Values in **bold** are significant at $p < 0.05$. Values in *italics* are significant at $p < 0.20$. Diagnosis is coded with higher values indicating more impairment. SES = socioeconomic status; APOE = Apolipoprotein E; Depression Sx = depression symptoms; BMI = body mass index; Sleep Frag = sleep fragmentation. N=446.

Table 14

Multiple Linear Regression Predicting Working Memory with Significant Demographics, Risk Factors, and Lifestyle Factors—Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Education	0.045	0.012	0.169	< 0.001	0.020	0.069
Early Life SES	0.108	0.047	0.104	0.023	0.015	0.201
Diet	0.036	0.017	0.094	0.035	0.003	0.070
Diagnosis	-0.445	0.065	-0.298	< 0.001	-0.573	-0.318
$R_2 = 0.178$; $R_{2Adj} = 0.171$; $F(4, 457) = 24.75$; $p < 0.001$						

Note. SES = socioeconomic status. Diagnosis is coded with higher values indicating more impairment. N=462.

Table 15

Multiple Linear Regression Predicting Global Cognition with Demographics, Risk Factors, and Lifestyle Factors in Individuals with No Cognitive Impairment–Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Age	-0.018	0.003	-0.295	< 0.001	-0.024	-0.013
Education	0.053	0.008	0.324	< 0.001	0.037	0.068
Sex (male)	-0.171	0.047	-0.164	< 0.001	-0.264	-0.079
Early Life SES	0.073	0.031	0.113	0.019	0.012	0.134
Social Activities	0.081	0.036	0.102	0.026	0.010	0.153
$R_2 = 0.305$; $R_{2Adj} = 0.295$; $F(5, 351) = 30.84$; $p < 0.001$						

Note. SES = socioeconomic status. This model includes only individuals with normal cognition at analytic baseline. N=357.

Table 16

Multiple Linear Regression Predicting Global Cognition with Significant Demographics, Risk Factors, and Lifestyle Factors in Impaired Individuals —Final Model

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
Education	0.063	0.016	0.337	<0.001	0.030	0.095
BMI	0.026	0.010	0.228	0.011	0.006	0.045
Diet	0.071	0.024	0.264	0.004	0.023	0.118
Physical Activity	0.094	0.030	0.275	0.003	0.034	0.154
$R_2 = 0.299$; $R_{2Adj} = 0.269$; $F(4, 92)= 9.82$; $p< 0.001$						

Note. BMI = body mass index. This model includes only individuals with an analytic baseline diagnosis of MCI or AD. N=97.

Table 17

Multiple Linear Regression Predicting Global Cognition with HS1

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS1	0.036	0.017	0.070	0.035	0.003	0.069
Age	-0.019	0.003	-0.241	< 0.001	-0.024	-0.014
Education	0.060	0.007	0.294	< 0.001	0.047	0.073
Sex (male)	-0.153	0.041	-0.121	< 0.001	-0.233	-0.073
Diagnosis	-0.584	0.038	-0.510	< 0.001	-0.659	-0.509
$R_2 = 0.541$; $R_{2Adj} = 0.536$; $F(5, 461) = 108.52$; $p < 0.001$						

Note. HS1 consists of social activities. HS = Health Score; Diagnosis is coded with higher values indicating more impairment.

Table 18

Multiple Linear Regression Predicting Global Cognition with HS2

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS2	0.021	0.008	0.090	0.007	0.006	0.036
Age	-0.019	0.003	-0.243	< 0.001	-0.024	-0.014
Education	0.059	0.007	0.287	< 0.001	0.046	0.072
Sex (male)	-0.140	0.041	-0.110	0.001	-0.220	-0.060
Diagnosis	-0.575	0.039	-0.502	< 0.001	-0.650	-0.499
$R_2 = 0.543$; $R_{2Adj} = 0.538$; $F(5, 461) = 109.70$; $p < 0.001$						

Note. HS2 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress). HS = Health Score; Diagnosis is coded with higher values indicating more impairment.

Table 19

Multiple Linear Regression Predicting Global Cognition with HS3

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS3	0.001	0.011	0.003	0.925	-0.020	0.022
Age	-0.020	0.003	-0.258	< 0.001	-0.025	-0.015
Education	0.061	0.007	0.306	< 0.001	0.048	0.074
Sex (male)	-0.167	0.042	-0.134	< 0.001	-0.249	-0.085
Diagnosis	-0.591	0.039	-0.510	< 0.001	-0.667	-0.514
$R_2 = 0.522$; $R_{2Adj} = 0.517$; $F(5, 445) = 97.18$; $p < 0.001$						

Note. HS3 consists of all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI).

HS = Health Score; Diagnosis is coded with higher values indicating more impairment.

Table 20

Multiple Linear Regression Predicting Global Cognition with HS4

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS4	0.013	0.006	0.076	0.024	0.002	0.025
Age	-0.020	0.003	-0.258	< 0.001	-0.025	-0.015
Education	0.060	0.007	0.297	< 0.001	0.047	0.073
Sex (male)	-0.158	0.042	-0.126	< 0.001	-0.240	-0.076
Diagnosis	-0.574	0.040	-0.495	< 0.001	-0.651	-0.496
$R_2 = 0.527$; $R_{2Adj} = 0.522$; $F(5, 445) = 99.33$; $p < 0.001$						

Note. HS4 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress) and all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). HS = Health Score; Diagnosis is coded with higher values indicating more impairment.

Table 21

Meng Tests of Model Comparison between Two Health Scores

Comparison of Model 1 & Model 2	Model 1 R^2	Model 2 R^2	z-value	*p*
HS1 & HS2	0.541	0.543	-1.572	0.116
HS1 & HS3	0.541	0.522	4.737	<0.001
HS1 & HS4	0.541	0.527	1.283	0.200
HS2 & HS3	0.543	0.522	6.036	<0.001
HS2 & HS4	0.543	0.527	4.900	<0.001
HS3 & HS4	0.522	0.527	-6.159	<0.001

Note. All models contained covariates (i.e., Age, Education, Sex, Diagnosis) and one Health Score (HS). HS1 consists of social activities. HS2 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress). HS3 consists of all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). HS4 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress) and all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). p-value is two-tailed.

Table 22

Multiple Linear Regression Predicting Global Cognition with HS1 for Normal Cognition

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS1	0.046	0.019	0.107	0.018	0.008	0.084
Age	-0.019	0.003	-0.298	< 0.001	-0.024	-0.013
Education	0.053	0.008	0.323	< 0.001	0.037	0.068
Sex	-0.171	0.047	-0.164	< 0.001	-0.264	-0.079
Early Life SES	0.076	0.031	0.118	0.015	0.015	0.137
$R_2 = 0.306$; $R_{2Adj} = 0.297$; $F(5, 351)= 30.01$; $p< 0.001$						

Note. HS1 consists of social activities. HS = Health Score; SES = socioeconomic status.

N=357.

Table 23

Multiple Linear Regression Predicting Global Cognition with HS2 for Normal Cognition

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS2	0.020	0.009	0.105	0.021	0.003	0.038
Age	-0.019	0.003	-0.308	< 0.001	-0.025	-0.014
Education	0.051	0.008	0.311	< 0.001	0.035	0.066
Sex	-0.160	0.047	-0.153	0.001	-0.253	-0.067
Early Life SES	0.074	0.031	0.115	0.017	0.013	0.135
$R_2 = 0.306$; $R_{2Adj} = 0.296$; $F(5, 351) = 30.94$; $p < 0.001$						

Note. HS2 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress). HS = Health Score; SES = socioeconomic status. N=357.

Table 24

Multiple Linear Regression Predicting Global Cognition with HS3 for Normal Cognition

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS3	0.008	0.012	0.030	0.520	-0.016	0.032
Age	-0.020	0.003	-0.321	< 0.001	-0.026	-0.014
Education	0.055	0.008	0.335	< 0.001	0.039	0.071
Sex	-0.183	0.049	-0.172	< 0.001	-0.278	-0.087
Early Life SES	0.072	0.032	0.111	0.023	0.010	0.134
$R_2 = 0.303$; $R_{2Adj} = 0.293$; $F(5, 344)= 29.96$; $p< 0.001$						

Note. HS3 consists of all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI).

HS = Health Score; SES = socioeconomic status. N=350.

Table 25

Multiple Linear Regression Predicting Global Cognition with HS4 for Normal Cognition

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS4	0.014	0.007	0.097	0.034	0.001	0.027
Age	-0.020	0.003	-0.320	< 0.001	-0.026	-0.015
Education	0.052	0.008	0.319	< 0.001	0.037	0.068
Sex	-0.174	0.049	-0.164	< 0.001	-0.270	-0.079
Early Life SES	0.075	0.031	0.116	0.016	0.014	0.137
R_2 =0.312; R_{2Adj} = 0.302; $F(5, 344)$= 31.14; p< 0.001						

Note. HS4 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress) and all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). HS = Health Score; SES = socioeconomic status. N=350.

Table 26

Multiple Linear Regression Predicting Global Cognition with HS1 for MCI and AD

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS1	0.026	0.045	0.053	0.573	-0.064	0.115
Age	-0.023	0.008	-0.259	0.007	-0.040	-0.007
Education	0.068	0.018	0.344	< 0.001	0.033	0.102
$R_2 = 0.186$; $R_{2Adj} = 0.162$; $F(3, 102) = 7.75$; $p < 0.001$						

Note. HS1 consists of social activities. HS = Health Score. The other covariates were not significant and thus removed from the model. N=106.

Table 27

Multiple Linear Regression Predicting Global Cognition with HS2 for MCI and AD

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS2	0.042	0.020	0.192	0.039	0.002	0.082
Age	-0.020	0.008	-0.220	0.018	-0.036	-0.003
Education	0.068	0.017	0.347	<0.001	0.034	0.102
$R_2 = 0.217$; $R_{2Adj} = 0.194$; $F(3, 102)= 9.41$; $p< 0.001$						

Note. HS2 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress). HS = Health Score. The other covariates were not significant and thus removed from the model. N=106.

Table 28

Multiple Linear Regression Predicting Global Cognition with HS3 for MCI and AD

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS3	-0.034	0.032	-0.104	0.278	-0.097	0.028
Age	-0.020	0.008	-0.229	0.017	-0.036	-0.004
Education	0.061	0.018	0.329	0.001	0.026	0.097
Sex	-0.197	0.099	-0.187	0.049	-0.394	-0.001
$R_2 = 0.208$; $R_{2Adj} = 0.174$; $F(4, 92) = 6.05$; $p < 0.001$						

Note. HS3 consists of all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). HS = Health Score. The other covariates were not significant and thus removed from the model. N=97.

Table 29

Multiple Linear Regression Predicting Global Cognition with HS4 for MCI and AD

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS4	0.022	0.017	0.130	0.177	-0.010	0.055
Age	-0.021	0.008	-0.245	0.012	-0.038	-0.005
Education	0.067	0.018	0.362	<0.001	0.032	0.103
$R_2 = 0.182$; $R_{2Adj} = 0.155$; $F(3, 93)= 6.89$; $p< 0.001$						

Note. HS4 consists of all five lifestyle factors (i.e., diet, physical activity, sleep fragmentation, social activities, perceived stress) and all five risk factors (i.e., depression, smoking, alcohol, APOE, BMI). HS = Health Score; SES = socioeconomic status. N=97.

Table 30

Multiple Linear Regression Predicting Global Cognition with HS1 for MCI and AD

					95% CI for B	
	B	Std Err	β_{stand}	*p*	Lower	Upper
HS1-Im	0.039	0.023	0.165	0.087	-0.006	0.084
Age	-0.020	0.008	-0.227	0.020	-0.036	-0.003
Education	0.063	0.018	0.339	0.001	0.028	0.098
$R_2 = 0.192$; $R_{2Adj} = 0.166$; $F(3, 93) = 7.35$; $p < 0.001$						

Note. HS1-Im was modified to include variables significantly predictive of global cognition exclusively in the impaired group and consisted of diet, physical activity, and BMI. HS = Health Score. Im = impaired. The other covariates were not significant and thus removed from the model. N=96.

Table 31

Mean Cognition Slope by Analytic Baseline Health Score Categories

	Full Sample	Unfavorable	Minimally Favorable	Moderately Favorable	Favorable
Global Cognition (n=111)	-0.038 (.079) [-0.2675 to 0.1404]	-0.049 (.068) n=24	-0.070 (.071) n=26	-0.029 (.096) n=28	-0.013 (.071) n=33
Verbal Memory (n=112)	-0.046 (.138) [-0.502 to 0.257]	-0.078 (.149) n=25	-0.079 (.144) n=26	-0.043 (.143) n=28	0.002 (.111) n=33
Processing Speed (n=109)	-0.069 (.114) [-0.4724 to 0.1905]	-0.061 (.122) n=23	-0.091 (.116) n=25	-0.049 (.112) n=28	-0.077 (.111) n=33
Working Memory (n=111)	-0.008 (.130) [-0.3747 to 0.4614]	-0.036 (.118) n=24	-0.041 (.141) n=26	0.014 (.123) n=28	0.019 (.130) n=33

Note. Mean (standard deviation) [range]; The Health Score in these analyses is HS2 (which includes diet, physical activity, social activities, sleep fragmentation and stress reduction).

Table 32

Mean Cognition Slope by Averaged Health Scores Categories

	Full Sample	Unfavorable	Minimally Favorable	Moderately Favorable	Favorable
Global Cognition (n=111)	-0.038 (.079) [-0.2675 to 0.1404]	-0.057 (.081) n=29	-0.049 (.075) n=26	-0.039 (.079) n=25	-0.010 (.077) n=31
Verbal Memory (n=112)	-0.046 (.138) [-0.502 to 0.257]	-0.082 (.152) n=30	-0.045 (.132) n=26	-0.040 (.131) n=25	-0.016 (.135) n=31
Processing Speed (n=109)	-0.069 (.114) [-0.4724 to 0.1905]	-0.067 (.133) n=29	-0.103 (.090) n=25	-0.076 (.135) n=24	-0.040 (.092) n=31
Working Memory (n=111)	-0.008 (.130) [-0.3747 to 0.4614]	-0.043 (.114) n=29	0.003 (.120) n=26	-0.032 (.120) n=25	0.034 (.151) n=31

Note. Mean (standard deviation) [range]; The Health Score in these analyses is HS2 (which includes diet, physical activity, social activities, sleep fragmentation and stress reduction).

Table 33

Summary of Analysis of Variance Models with Health Score at Analytic Baseline

Cognition Slope	F	*p*	Partial Eta Squared	Observed Power
Global Cognition	2.835	0.042	0.074	0.666
Verbal Memory	2.360	0.076	0.062	0.578
Processing Speed	0.645	0.588	0.018	0.181
Working Memory	3.606	0.009*	0.120	0.861

Note. This table lists the summary statistics for each omnibus ANOVA model. Each model consists of HS2 categories (independent variable) predicting rate of cognitive change (i.e., cognition slope; dependent variable).

*The model for Working Memory is an Analysis of Covariance with Age as a significant covariate. While Age had a significant *p*-value (*p*=0.004), the Health Score was not a significant predictor (*p*=0.182).

Table 34

Summary of Analysis of Variance Models with Averaged Health Score

Cognition Slope	F	*p*	Partial Eta Squared	Observed Power
Global Cognition	2.050	0.111	0.054	0.513
Verbal Memory	1.164	0.327	0.031	0.306
Processing Speed	1.436	0.236	0.039	0.371
Working Memory	3.631	0.008*	0.120	0.863

Note. This table lists the summary statistics for each omnibus ANOVA model. Each model consists of HS2 categories (independent variable) predicting rate of cognitive change (i.e., cognition slope; dependent variable).

*The model for Working Memory is an Analysis of Covariance with Age as a significant covariate. While Age had a significant *p*-value (*p*=0.007), the Health Score was not a significant predictor (*p*=0.175).

APPENDICES

Appendix A

MIND Diet Components

Diet Component	0	0.5	1
Green leafy vegetables	≤2 servings/week	>2 to <6 servings/week	≥6 servings/week
Other vegetables	<5 servings/week	5-6 servings/week	≥1 serving/day
Berries	<1 servings/week	1 serving/week	≥2 servings/week
Nuts	<0.5 servings/week	0.5-4 servings/week	≥5 servings/week
Olive oil	Not primary oil	X	Primary oil used
Butter, margarine	>2 teaspoons/day	1-2 teaspoons/day	<1 teaspoon/day
Cheese	≥7 servings/week	1 -6 servings/week	<1 serving/week
Whole grains	<1 servings/day	1-2 servings/day	≥3 servings/day
Fish (not fried)	<1 meal/month	1-3 meals/month	≥1 meals/week
Beans	<1 meal/month	1-3 meals/week	>3 meals/week
Poultry (not fried)	<1 meal/month	1 meal per week	≥2 meals/week
Red meat and products	>6 meals/week	4-6 meals/week	<4 meals/week
Fast fried foods	>3 times/week	1-3 times/week	<1 time/week
Pastries and sweets	≥7 servings/week	5-6 servings/week	<5 servings/week
Wine	<1 glass/month or ≥2 glasses/day	1 glass/month to 1 glass/week	2-7 glasses/week

(Range: 0-15)

Appendix B

Social Activities Questionnaire

During the past year, how often did you…	Once a year or less	Several times a year	Several times a month	Several times a week	Every day or almost every day
1. go to restaurants, sporting events or teletract, or play bingo?	1	2	3	4	5
2. go on day trips or overnight trips?	1	2	3	4	5
3. do unpaid community/volunteer work?	1	2	3	4	5
4. visit at relatives' or friends' houses?	1	2	3	4	5
5. participate in groups (such as senior center, VFW, Knights of Columbus, Rosary Society or something similar)*?	1	2	3	4	5
6. attend church or religious services?	1	2	3	4	5
*VFW is the Veterans of Foreign Wars national organization that has social programs. Knights of Columbus and the Rosary Society are both catholic organization that have a social component.					

Appendix C

Perceived Stress Scale

In the past month, how often have you felt…	Never	Almost never	Some-times	Fairly often	Very often
1. that you were unable to control the important things in your life?	0	1	2	3	4
2. confident about your ability to handle your personal problems?*	0	1	2	3	4
3. that things were going your way?*	0	1	2	3	4
4. difficulties were piling up so high that you could not overcome them?	0	1	2	3	4
*Questions 2 and 3 are reversed so that higher scores indicate more perceived stress across all items. PSS score is the average score of responses to all 4 questions.					

Appendix D

Center for Epidemiologic Studies Depression Scale (CES-D-10)

Center for Epidemiologic Studies Depression Scale (CES-D-10)

Below is a list of some of the ways you may have felt or behaved.

Please indicate if you have felt this way during the past week by circling Yes or No for each question.

1	I felt depressed.	Yes	No
2	I felt that everything I did was an effort.	Yes	No
3	My sleep was restless.	Yes	No
4*	I was happy.	Yes	No
5	I felt lonely.	Yes	No
6	People were unfriendly.	Yes	No
7*	I enjoyed life.	Yes	No
8	I felt sad.	Yes	No
9	I felt that people disliked me.	Yes	No
10	I could not get going.	Yes	No

*One point is granted for each Yes response except for items 4 and 7, which are reverse scored, such that a No response is given one point on those two items.

REFERENCES

2015–2020 Dietary Guidelines for Americans, (2015).

Adam, K., & Oswald, I. (1977). Sleep is for tissue restoration. *J R Coll Physicians Lond, 11*(4), 376-388. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/328867

Adorni, R., Brugnera, A., Gatti, A., Tasca, G. A., Sakatani, K., & Compare, A. (2019). Psychophysiological Responses to Stress Related to Anxiety in Healthy Aging. *Journal of Psychophysiology, 33*(3), 188-197. doi:10.1027/0269-8803/a000221

Aggarwal, N. T., Wilson, R. S., Beck, T. L., Rajan, K. B., Mendes de Leon, C. F., Evans, D. A., & Everson-Rose, S. A. (2014). Perceived stress and change in cognitive function among adults 65 years and older. *Psychosom Med, 76*(1), 80-85. doi:10.1097/PSY.0000000000000016

Akbaraly, T. N., Singh-Manoux, A., Dugravot, A., Brunner, E. J., Kivimaki, M., & Sabia, S. (2019). Association of Midlife Diet With Subsequent Risk for Dementia. *JAMA, 321*(10), 957-968. doi:10.1001/jama.2019.1432

Albert, M., Smith, L. A., Scherr, P. A., Taylor, J. O., Evans, D. A., & Funkenstein, H. H. (1991). Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J Neurosci, 57*(3-4), 167-178. doi:10.3109/00207459109150691

Anastasiou, C. A., Yannakoulia, M., Kontogianni, M. D., Kosmidis, M. H., Mamalaki, E., Dardiotis, E., . . . Scarmeas, N. (2018). Mediterranean Lifestyle in Relation to Cognitive Health: Results from the HELIAD Study. *Nutrients, 10*(10). doi:10.3390/nu10101557

Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., . . . Group, M. S. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or

without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol, 16*(5), 377-389. doi:10.1016/S1474-4422(17)30040-6

Appel, L. J., Brands, M. W., Daniels, S. R., Karanja, N., Elmer, P. J., Sacks, F. M., & American Heart, A. (2006). Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension, 47*(2), 296-308. doi:10.1161/01.HYP.0000202568.01167.B6

Ardura-Fabregat, A., Boddeke, E., Boza-Serrano, A., Brioschi, S., Castro-Gomez, S., Ceyzeriat, K., . . . Yang, Y. (2017). Targeting Neuroinflammation to Treat Alzheimer's Disease. *CNS Drugs, 31*(12), 1057-1082. doi:10.1007/s40263-017-0483-3

Ashby-Mitchell, K., Burns, R., Shaw, J., & Anstey, K. J. (2017). Proportion of dementia in Australia explained by common modifiable risk factors. *Alzheimers Res Ther, 9*(1), 11. doi:10.1186/s13195-017-0238-x

Association, A. s. (2019). 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 15*(3), 321-387. doi:10.1016/j.jalz.2019.01.010

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., . . . Craft, S. (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol, 67*(1), 71-79. doi:10.1001/archneurol.2009.307

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement, 11*(6), 718-726. doi:10.1016/j.jalz.2015.05.016

Beller, J., & Wagner, A. (2018). Loneliness, social isolation, their synergistic interaction, and mortality. *Health Psychol, 37*(9), 808-813. doi:10.1037/hea0000605

Bennett, D. A., Schneider, J. A., Buchman, A. S., Barnes, L. L., Boyle, P. A., & Wilson, R. S. (2012). Overview and findings from the rush Memory and Aging Project. *Curr Alzheimer Res, 9*(6), 646-663. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22471867

Bennett, D. A., Schneider, J. A., Buchman, A. S., Mendes de Leon, C., Bienias, J. L., & Wilson, R. S. (2005). The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology, 25*(4), 163-175. doi:10.1159/000087446

Bennett, D. A., Schneider, J. A., Tang, Y., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol, 5*(5), 406-412. doi:10.1016/s1474-4422(06)70417-3

Benton, A. L., Varney, N. R., & Hamsher, K. D. (1978). Visuospatial judgment. A clinical test. *Arch Neurol, 35*(6), 364-367. doi:10.1001/archneur.1978.00500300038006

Berendsen, A., Santoro, A., Pini, E., Cevenini, E., Ostan, R., Pietruszka, B., . . . de Groot, C. P. (2014). Reprint of: A parallel randomized trial on the effect of a healthful diet on inflammageing and its consequences in European elderly people: design of the NU-AGE dietary intervention study. *Mech Ageing Dev, 136-137*, 14-21. doi:10.1016/j.mad.2014.03.001

Berendsen, A. A., Kang, J. H., van de Rest, O., Jankovic, N., Kampman, E., Kiefte-de Jong, J. C., . . . de Groot, L. C. (2017). Association of Adherence to a Healthy Diet with Cognitive Decline in European and American Older Adults: A Meta-Analysis within the

CHANCES Consortium. *Dement Geriatr Cogn Disord, 43*(3-4), 215-227. doi:10.1159/000464269

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Soc Sci Med, 51*(6), 843-857. doi:10.1016/s0277-9536(00)00065-4

Berti, V., Walters, M., Sterling, J., Quinn, C. G., Logue, M., Andrews, R., . . . Mosconi, L. (2018). Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. *Neurology, 90*(20), e1789-e1798. doi:10.1212/WNL.0000000000005527

Blackwell, T., Yaffe, K., Ancoli-Israel, S., Redline, S., Ensrud, K. E., Stefanick, M. L., . . . Osteoporotic Fractures in Men Study, G. (2011). Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. *Sleep, 34*(10), 1347-1356. doi:10.5665/SLEEP.1276

Blazer, D. G. (2003). Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci, 58*(3), 249-265. doi:10.1093/gerona/58.3.m249

Blumenthal, J. A., Smith, P. J., Mabe, S., Hinderliter, A., Lin, P. H., Liao, L., . . . Sherwood, A. (2019). Lifestyle and neurocognition in older adults with cognitive impairments: A randomized trial. *Neurology, 92*(3), e212-e223. doi:10.1212/WNL.0000000000006784

Blumenthal, J. A., Smith, P. J., Mabe, S., Hinderliter, A., Welsh-Bohmer, K., Browndyke, J. N., . . . Sherwood, A. (2017). Lifestyle and Neurocognition in Older Adults With Cardiovascular Risk Factors and Cognitive Impairment. *Psychosom Med, 79*(6), 719-727. doi:10.1097/PSY.0000000000000474

Bos, I., Vos, S. J., Frolich, L., Kornhuber, J., Wiltfang, J., Maier, W., . . . Visser, P. J. (2017). The frequency and influence of dementia risk factors in prodromal Alzheimer's disease. *Neurobiol Aging, 56*, 33-40. doi:10.1016/j.neurobiolaging.2017.03.034

Bott, N., Kumar, S., Krebs, C., Glenn, J. M., Madero, E. N., & Juusola, J. L. (2018). A Remote Intervention to Prevent or Delay Cognitive Impairment in Older Adults: Design, Recruitment, and Baseline Characteristics of the Virtual Cognitive Health (VC Health) Study. *JMIR Res Protoc, 7*(8), e11368. doi:10.2196/11368

Bott, N. T., Hall, A., Madero, E. N., Glenn, J. M., Fuseya, N., Gills, J. L., & Gray, M. (2019). Face-to-Face and Digital Multidomain Lifestyle Interventions to Enhance Cognitive Reserve and Reduce Risk of Alzheimer's Disease and Related Dementias: A Review of Completed and Prospective Studies. *Nutrients, 11*(9). doi:10.3390/nu11092258

Brandt, J., Buchholz, A., Henry-Barron, B., Vizthum, D., Avramopoulos, D., & Cervenka, M. C. (2019). Preliminary Report on the Feasibility and Efficacy of the Modified Atkins Diet for Treatment of Mild Cognitive Impairment and Early Alzheimer's Disease. *J Alzheimers Dis, 68*(3), 969-981. doi:10.3233/JAD-180995

Braveman, P., Egerter, S., & Williams, D. R. (2011). The social determinants of health: coming of age. *Annu Rev Public Health, 32*, 381-398. doi:10.1146/annurev-publhealth-031210-101218

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement, 3*(3), 186-191. doi:10.1016/j.jalz.2007.04.381

Brown, C. L., Robitaille, A., Zelinski, E. M., Dixon, R. A., Hofer, S. M., & Piccinin, A. M. (2016). Cognitive activity mediates the association between social activity and cognitive

performance: A longitudinal study. *Psychol Aging, 31*(8), 831-846. doi:10.1037/pag0000134

Bubu, O. M., Brannick, M., Mortimer, J., Umasabor-Bubu, O., Sebastiao, Y. V., Wen, Y., . . . Anderson, W. M. (2017). Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. *Sleep, 40*(1). doi:10.1093/sleep/zsw032

Buchman, A. S., Boyle, P. A., Yu, L., Shah, R. C., Wilson, R. S., & Bennett, D. A. (2012). Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology, 78*(17), 1323-1329. doi:10.1212/WNL.0b013e3182535d35

Buchman, A. S., Wilson, R. S., & Bennett, D. A. (2008). Total daily activity is associated with cognition in older persons. *Am J Geriatr Psychiatry, 16*(8), 697-701. doi:10.1097/JGP.0b013e31817945f6

Buchman, A. S., Wilson, R. S., Bienias, J. L., Shah, R. C., Evans, D. A., & Bennett, D. A. (2005). Change in body mass index and risk of incident Alzheimer disease. *Neurology, 65*(6), 892-897. doi:10.1212/01.wnl.0000176061.33817.90

Byrne, A., & Byrne, D. G. (1993). The effect of exercise on depression, anxiety and other mood states: A review. *Journal of Psychosomatic Research, 37*(6), 565-574. doi:https://doi.org/10.1016/0022-3999(93)90050-P

Cai, H., Li, G., Hua, S., Liu, Y., & Chen, L. (2017). Effect of exercise on cognitive function in chronic disease patients: a meta-analysis and systematic review of randomized controlled trials. *Clin Interv Aging, 12*, 773-783. doi:10.2147/CIA.S135700

Calamia, M., De Vito, A., Bernstein, J. P. K., Weitzner, D. S., Carmichael, O. T., & Keller, J. N. (2018). Pedometer-assessed steps per day as a predictor of cognitive performance in older adults. *Neuropsychology, 32*(8), 941-949. doi:10.1037/neu0000487

Calil, S. R. B., Brucki, S. M. D., Nitrini, R., & Yassuda, M. S. (2018). Adherence to the Mediterranean and MIND diets is associated with better cognition in healthy seniors but not in MCI or AD. *Clin Nutr ESPEN, 28*, 201-207. doi:10.1016/j.clnesp.2018.08.001

Campos, M. W., Serebrisky, D., & Castaldelli-Maia, J. M. (2016). Smoking and Cognition. *Curr Drug Abuse Rev, 9*(2), 76-79. doi:10.2174/1874473709666160803101633

Carnethon, M. R., Kershaw, K. N., & Kandula, N. R. (2019). Disparities Research, Disparities Researchers, and Health Equity. *JAMA*. doi:10.1001/jama.2019.19329

Carvalho, A., Rea, I. M., Parimon, T., & Cusack, B. J. (2014). Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clin Interv Aging, 9*, 661-682. doi:10.2147/CIA.S55520

Castellano, C. A., Nugent, S., Paquet, N., Tremblay, S., Bocti, C., Lacombe, G., . . . Cunnane, S. C. (2015). Lower brain 18F-fluorodeoxyglucose uptake but normal 11C-acetoacetate metabolism in mild Alzheimer's disease dementia. *J Alzheimers Dis, 43*(4), 1343-1353. doi:10.3233/JAD-141074

Cervenka, M. C., Patton, K., Eloyan, A., Henry, B., & Kossoff, E. H. (2016). The impact of the modified Atkins diet on lipid profiles in adults with epilepsy. *Nutritional Neuroscience, 19*(3), 131-137. doi:10.1179/1476830514Y.0000000162

Chavannes, N., Vollenberg, J. J., van Schayck, C. P., & Wouters, E. F. (2002). Effects of physical activity in mild to moderate COPD: a systematic review. *Br J Gen Pract, 52*(480), 574-578. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12120732

Chen, Y., Wang, J., Liang, Y., Sun, F., & Dong, X. (2018). Perceived Stress and Cognitive Functions Among Chinese Older Adults: The Moderating Role of Health Status. *Gerontol Geriatr Med, 4*, 2333721418778390. doi:10.1177/2333721418778390

Cherbuin, N., & Anstey, K. J. (2012). The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH Through Life study. *Am J Geriatr Psychiatry, 20*(7), 635-639. doi:10.1097/JGP.0b013e31823032a9

Cho, H., Kim, C., Kim, H. J., Ye, B. S., Kim, Y. J., Jung, N. Y., . . . Seo, S. W. (2016). Impact of smoking on neurodegeneration and cerebrovascular disease markers in cognitively normal men. *Eur J Neurol, 23*(1), 110-119. doi:10.1111/ene.12816

Chodzko-Zajko, W. J. (1991). Physical fitness, cognitive performance, and aging. *Medicine & Science in Sports & Exercise*.

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nat Rev Endocrinol, 5*(7), 374-381. doi:10.1038/nrendo.2009.106

Clarkson-Smith, L., & Hartley, A. A. (1989). Relationships between physical exercise and cognitive abilities in older adults. *Psychology and aging, 4*(2), 183.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/6668417

Cohen, S., & Williamson, G. (1988). Perceived stress in a probability sample of the United States. In S. Spacapan & S. Oskamp (Eds.), *The social psychology of health* (pp. 251 p.). Newbury Park, Calif.: Sage Publications.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci, 14*(2), 125-130. doi:10.1111/1467-9280.t01-1-01430

Conn, V. S., Hafdahl, A. R., Porock, D. C., McDaniel, R., & Nielsen, P. J. (2006). A meta-analysis of exercise interventions among people treated for cancer. *Supportive Care in Cancer, 14*(7), 699-712. doi:10.1007/s00520-005-0905-5

Cooper, C., Sommerlad, A., Lyketsos, C. G., & Livingston, G. (2015). Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry, 172*(4), 323-334. doi:10.1176/appi.ajp.2014.14070878

Cooper, J. A., & Sagar, H. J. (1993). Incidental and intentional recall in Parkinson's disease: an account based on diminished attentional resources. *J Clin Exp Neuropsychol, 15*(5), 713-731. doi:10.1080/01688639308402591

Cosentino, S., Scarmeas, N., Helzner, E., Glymour, M. M., Brandt, J., Albert, M., . . . Stern, Y. (2008). APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. *Neurology, 70*(19 Pt 2), 1842-1849. doi:10.1212/01.wnl.0000304038.37421.cc

Cournot, M., Marquie, J. C., Ansiau, D., Martinaud, C., Fonds, H., Ferrieres, J., & Ruidavets, J. B. (2006). Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology, 67*(7), 1208-1214. doi:10.1212/01.wnl.0000238082.13860.50

Crittenden, C. N., Murphy, M. L. M., & Cohen, S. (2018). Social integration and age-related decline in lung function. *Health Psychol, 37*(5), 472-480. doi:10.1037/hea0000592

Croteau, E., Castellano, C. A., Fortier, M., Bocti, C., Fulop, T., Paquet, N., & Cunnane, S. C. (2018). A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Exp Gerontol, 107*, 18-26. doi:10.1016/j.exger.2017.07.004

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther, 6*(4), 37. doi:10.1186/alzrt269

Cummings, J. L., Tong, G., & Ballard, C. (2019). Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *J Alzheimers Dis, 67*(3), 779-794. doi:10.3233/JAD-180766

Dause, T. J., & Kirby, E. D. (2019). Aging gracefully: social engagement joins exercise and enrichment as a key lifestyle factor in resistance to age-related cognitive decline. *Neural Regen Res, 14*(1), 39-42. doi:10.4103/1673-5374.243698

Davis, C., Bryan, J., Hodgson, J., & Murphy, K. (2015). Definition of the Mediterranean Diet; a Literature Review. *Nutrients, 7*(11), 9139-9153. doi:10.3390/nu7115459

Deak, M. C., & Stickgold, R. (2010). Sleep and cognition. *Wiley Interdiscip Rev Cogn Sci, 1*(4), 491-500. doi:10.1002/wcs.52

Di Marco, L. Y., Marzo, A., Munoz-Ruiz, M., Ikram, M. A., Kivipelto, M., Ruefenacht, D., . . . Frangi, A. F. (2014). Modifiable lifestyle factors in dementia: a systematic review of longitudinal observational cohort studies. *J Alzheimers Dis, 42*(1), 119-135. doi:10.3233/JAD-132225

Diehl, M., Smyer, M. A., & Mehrotra, C. M. (2020). Optimizing aging: A call for a new narrative. *Am Psychol, 75*(4), 577-589. doi:10.1037/amp0000598

Dustman, R. E., Ruhling, R. O., Russell, E. M., Shearer, D. E., Bonekat, H. W., Shigeoka, J. W., . . . Bradford, D. C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of aging, 5*(1), 35-42.

Eggermont, L., Swaab, D., Luiten, P., & Scherder, E. (2006). Exercise, cognition and Alzheimer's disease: more is not necessarily better. *Neurosci Biobehav Rev, 30*(4), 562-575. doi:10.1016/j.neubiorev.2005.10.004

Ekstrom, R. B., Dermen, D., & Harman, H. H. (1976). *Manual for kit of factor-referenced cognitive tests* (Vol. 102): Educational testing service Princeton, NJ.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi:10.1073/pnas.1015950108

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002a). The role of stress in neurodegenerative diseases and mental disorders. *Neuro Endocrinol Lett, 23*(3), 199-208. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12080279

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002b). Stress in cardiovascular diseases. *Med Sci Monit, 8*(5), RA93-RA101. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12011786

Etnier, J. L., Karper, W. B., Labban, J. D., Piepmeier, A. T., Shih, C. H., Dudley, W. N., . . . Wideman, L. (2018). The Physical Activity and Alzheimer's Disease (PAAD) Study: Cognitive outcomes. *Ann Behav Med, 52*(2), 175-185. doi:10.1093/abm/kax035

Fani Marvasti, F., & Stafford, R. S. (2012). From sick care to health care--reengineering prevention into the U.S. system. *N Engl J Med, 367*(10), 889-891. doi:10.1056/NEJMp1206230

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., . . . van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA, 278*(16), 1349-1356.

Feart, C., Samieri, C., Rondeau, V., Amieva, H., Portet, F., Dartigues, J. F., . . . Barberger-Gateau, P. (2009). Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. *JAMA, 302*(6), 638-648. doi:10.1001/jama.2009.1146

Flatt, J. D., Hughes, T. F., Documet, P. I., Lingler, J. H., Trauth, J. M., & Albert, S. M. (2015). A Qualitative Study on the Types and Purposes of Social Activities in Late Life. *Act Adapt Aging, 39*(2), 109-132. doi:10.1080/01924788.2015.1024485

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1202204

Fonteh, A. (2018). Reasons Why Omega-3 Polyunsaturated Fatty Acids Produce Mixed Results in Alzheimer's Disease.

Forte, R., Pesce, C., De Vito, G., & Boreham, C. A. (2017). The Body Fat-Cognition Relationship in Healthy Older Individuals: Does Gynoid vs Android Distribution Matter? *J Nutr Health Aging, 21*(3), 284-291. doi:10.1007/s12603-016-0783-1

Fryar, C. D., Chen, T. C., & Li, X. (2012). Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010. *NCHS Data Brief*(103), 1-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23101933

Galvin, J. E. (2017). Prevention of Alzheimer's Disease: Lessons Learned and Applied. *J Am Geriatr Soc, 65*(10), 2128-2133. doi:10.1111/jgs.14997

Ganguli, M., Vander Bilt, J., Saxton, J. A., Shen, C., & Dodge, H. H. (2005). Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology, 65*(8), 1210-1217. doi:10.1212/01.wnl.0000180520.35181.24

Garcia-Ptacek, S., Faxen-Irving, G., Cermakova, P., Eriksdotter, M., & Religa, D. (2014). Body mass index in dementia. *Eur J Clin Nutr, 68*(11), 1204-1209. doi:10.1038/ejcn.2014.199

Gates, N., Fiatarone Singh, M. A., Sachdev, P. S., & Valenzuela, M. (2013). The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatry, 21*(11), 1086-1097. doi:10.1016/j.jagp.2013.02.018

Goodglass, H., & Kaplan, E. (1972). *The assessment of aphasia and related disorders*: Lea & Febiger.

Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H., & Campbell, J. L. (2008). The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 23*(5), 631-640. doi:10.1002/mds.21922

Gow, A. J., Corley, J., Starr, J. M., & Deary, I. J. (2013). Which social network or support factors are associated with cognitive abilities in old age? *Gerontology, 59*(5), 454-463. doi:10.1159/000351265

Graham, A. J., Martin-Ruiz, C. M., Teaktong, T., Ray, M. A., & Court, J. A. (2002). Human brain nicotinic receptors, their distribution and participation in neuropsychiatric disorders. *Curr Drug Targets CNS Neurol Disord, 1*(4), 387-397. doi:10.2174/1568007023339283

Greenfield, E. A., & Moorman, S. M. (2019). Childhood Socioeconomic Status and Later Life Cognition: Evidence From the Wisconsin Longitudinal Study. *J Aging Health, 31*(9), 1589-1615. doi:10.1177/0898264318783489

Grippo, A. J., & Johnson, A. K. (2009). Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress, 12*(1), 1-21. doi:10.1080/10253890802046281

Gualtieri, C. T., Johnson, L. G., & Benedict, K. B. (2006). Neurocognition in depression: patients on and off medication versus healthy comparison subjects. *J Neuropsychiatry Clin Neurosci, 18*(2), 217-225. doi:10.1176/jnp.2006.18.2.217

Gustafson, D. R., Backman, K., Joas, E., Waern, M., Ostling, S., Guo, X., & Skoog, I. (2012). 37 years of body mass index and dementia: observations from the prospective population study of women in Gothenburg, Sweden. *J Alzheimers Dis, 28*(1), 163-171. doi:10.3233/JAD-2011-110917

Hammen, C. (2005). Stress and depression. *Annu Rev Clin Psychol, 1*, 293-319. doi:10.1146/annurev.clinpsy.1.102803.143938

Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., & Pipingas, A. (2016). Adherence to a Mediterranean-Style Diet and Effects on Cognition in Adults: A Qualitative Evaluation and Systematic Review of Longitudinal and Prospective Trials. *Front Nutr, 3*, 22. doi:10.3389/fnut.2016.00022

Haslam, C., Cruwys, T., & Haslam, S. A. (2014). "The we's have it": evidence for the distinctive benefits of group engagement in enhancing cognitive health in aging. *Soc Sci Med, 120*, 57-66. doi:10.1016/j.socscimed.2014.08.037

He, X. F., Liu, D. X., Zhang, Q., Liang, F. Y., Dai, G. Y., Zeng, J. S., . . . Lan, Y. (2017). Voluntary Exercise Promotes Glymphatic Clearance of Amyloid Beta and Reduces the Activation of Astrocytes and Microglia in Aged Mice. *Front Mol Neurosci, 10*, 144. doi:10.3389/fnmol.2017.00144

Henderson, S. T., Vogel, J. L., Barr, L. J., Garvin, F., Jones, J. J., & Costantini, L. C. (2009). Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond), 6*, 31. doi:10.1186/1743-7075-6-31

Hernandez, S. S., Sandreschi, P. F., da Silva, F. C., Arancibia, B. A., da Silva, R., Gutierres, P. J., & Andrade, A. (2015). What are the Benefits of Exercise for Alzheimer's Disease? A Systematic Review of the Past 10 Years. *J Aging Phys Act, 23*(4), 659-668. doi:10.1123/japa.2014-0180

Hersi, M., Irvine, B., Gupta, P., Gomes, J., Birkett, N., & Krewski, D. (2017). Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. *Neurotoxicology, 61*, 143-187. doi:10.1016/j.neuro.2017.03.006

Hodes, R. J., & Bernard, M. A. (2020). Combatting racial inequality in aging research. Retrieved from https://www.nia.nih.gov/research/blog/2020/06/combatting-racial-inequality-aging-research?utm_source=NIA+Main&utm_campaign=67483351bb-20200617_blog&utm_medium=email&utm_term=0_ffe42fdac3-67483351bb-18459943

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS Med, 7*(7), e1000316. doi:10.1371/journal.pmed.1000316

Horder, H., Johansson, L., Guo, X., Grimby, G., Kern, S., & Skoog, I. (2018). Author response: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women. *Neurology, 91*(16), 763. doi:10.1212/WNL.0000000000006350

Hosking, D. E., Eramudugolla, R., Cherbuin, N., & Anstey, K. J. (2019). MIND not Mediterranean diet related to 12-year incidence of cognitive impairment in an Australian

longitudinal cohort study. *Alzheimers Dement, 15*(4), 581-589. doi:10.1016/j.jalz.2018.12.011

Hsiao, Y. H., Hung, H. C., Chen, S. H., & Gean, P. W. (2014). Social interaction rescues memory deficit in an animal model of Alzheimer's disease by increasing BDNF-dependent hippocampal neurogenesis. *J Neurosci, 34*(49), 16207-16219. doi:10.1523/JNEUROSCI.0747-14.2014

Hunter, J. C., Handing, E. P., Casanova, R., Kuchibhatla, M., Lutz, M. W., Saldana, S., . . . Hayden, K. M. (2018). Neighborhoods, sleep quality, and cognitive decline: Does where you live and how well you sleep matter? *Alzheimers Dement, 14*(4), 454-461. doi:10.1016/j.jalz.2017.10.007

Irwin, M., Artin, K. H., & Oxman, M. N. (1999). Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Arch Intern Med, 159*(15), 1701-1704. doi:10.1001/archinte.159.15.1701

Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A., & Cole, S. (2006). Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med, 166*(16), 1756-1762. doi:10.1001/archinte.166.16.1756

James, B. D., Boyle, P. A., Buchman, A. S., & Bennett, D. A. (2011). Relation of late-life social activity with incident disability among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci, 66*(4), 467-473. doi:10.1093/gerona/glq231

James, B. D., Wilson, R. S., Barnes, L. L., & Bennett, D. A. (2011). Late-life social activity and cognitive decline in old age. *J Int Neuropsychol Soc, 17*(6), 998-1005. doi:10.1017/S1355617711000531

Jiang, J. M., Seng, E. K., Zimmerman, M. E., Kim, M., & Lipton, R. B. (2017). Positively worded subscale score of the Perceived Stress Scale is associated with cognitive domain function. *J Behav Brain Sci, 7*(7), 311-324. doi:10.4236/jbbs.2017.77023

Jiang, X., Huang, J., Song, D., Deng, R., Wei, J., & Zhang, Z. (2017). Increased Consumption of Fruit and Vegetables Is Related to a Reduced Risk of Cognitive Impairment and Dementia: Meta-Analysis. *Front Aging Neurosci, 9*, 18. doi:10.3389/fnagi.2017.00018

Jones, K. D., Adams, D., Winters-Stone, K., & Burckhardt, C. S. (2006). A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988–2005). *Health and Quality of Life Outcomes, 4*(1), 67. doi:10.1186/1477-7525-4-67

Ju, Y. E., Lucey, B. P., & Holtzman, D. M. (2014). Sleep and Alzheimer disease pathology--a bidirectional relationship. *Nat Rev Neurol, 10*(2), 115-119. doi:10.1038/nrneurol.2013.269

Ju, Y. E., McLeland, J. S., Toedebusch, C. D., Xiong, C., Fagan, A. M., Duntley, S. P., . . . Holtzman, D. M. (2013). Sleep quality and preclinical Alzheimer disease. *JAMA Neurol, 70*(5), 587-593. doi:10.1001/jamaneurol.2013.2334

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). Boston Naming Test. Philadelphia, Lee and Febiger. In: Inc.

Karp, A., Paillard-Borg, S., Wang, H. X., Silverstein, M., Winblad, B., & Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord, 21*(2), 65-73. doi:10.1159/000089919

Kats, D., Patel, M. D., Palta, P., Meyer, M. L., Gross, A. L., Whitsel, E. A., . . . Heiss, G. (2016). Social support and cognition in a community-based cohort: the Atherosclerosis Risk in Communities (ARIC) study. *Age Ageing, 45*(4), 475-480. doi:10.1093/ageing/afw060

Katz, M. J., Derby, C. A., Wang, C., Sliwinski, M. J., Ezzati, A., Zimmerman, M. E., . . . Lipton, R. B. (2016). Influence of Perceived Stress on Incident Amnestic Mild Cognitive Impairment: Results From the Einstein Aging Study. *Alzheimer Dis Assoc Disord, 30*(2), 93-98. doi:10.1097/WAD.0000000000000125

Khansari, D. N., Murgo, A. J., & Faith, R. E. (1990). Effects of stress on the immune system. *Immunol Today, 11*(5), 170-175. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2186751

Kilander, L., Nyman, H., Boberg, M., & Lithell, H. (1997). Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. *J Intern Med, 242*(4), 313-321. doi:10.1046/j.1365-2796.1997.00196.x

Kim, J., Basak, J. M., & Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. *Neuron, 63*(3), 287-303. doi:10.1016/j.neuron.2009.06.026

Kim, S., Kim, Y., & Park, S. M. (2016). Body Mass Index and Decline of Cognitive Function. *PLoS One, 11*(2), e0148908. doi:10.1371/journal.pone.0148908

Kohout, F. J., Berkman, L. F., Evans, D. A., & Cornoni-Huntley, J. (1993). Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health, 5*(2), 179-193. doi:10.1177/089826439300500202

Korten, N. C., Sliwinski, M. J., Comijs, H. C., & Smyth, J. M. (2014). Mediators of the relationship between life events and memory functioning in a community sample of adults. *Appl Cogn Psychol, 28*(5), 626-633. doi:10.1002/acp.3043

Kossoff, E. H., Rowley, H., Sinha, S. R., & Vining, E. P. (2008). A prospective study of the modified Atkins diet for intractable epilepsy in adults. *Epilepsia, 49*(2), 316-319. doi:10.1111/j.1528-1167.2007.01256.x

Kotwal, A. A., Kim, J., Waite, L., & Dale, W. (2016). Social Function and Cognitive Status: Results from a US Nationally Representative Survey of Older Adults. *J Gen Intern Med, 31*(8), 854-862. doi:10.1007/s11606-016-3696-0

Krell-Roesch, J., Feder, N. T., Roberts, R. O., Mielke, M. M., Christianson, T. J., Knopman, D. S., . . . Geda, Y. E. (2018). Leisure-Time Physical Activity and the Risk of Incident Dementia: The Mayo Clinic Study of Aging. *J Alzheimers Dis, 63*(1), 149-155. doi:10.3233/JAD-171141

Krell-Roesch, J., Pink, A., Roberts, R. O., Stokin, G. B., Mielke, M. M., Spangehl, K. A., . . . Geda, Y. E. (2016). Timing of Physical Activity, Apolipoprotein E epsilon4 Genotype, and Risk of Incident Mild Cognitive Impairment. *J Am Geriatr Soc, 64*(12), 2479-2486. doi:10.1111/jgs.14402

Krikorian, R., Shidler, M. D., Dangelo, K., Couch, S. C., Benoit, S. C., & Clegg, D. J. (2012). Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiol Aging, 33*(2), 425 e419-427. doi:10.1016/j.neurobiolaging.2010.10.006

Krueger, K. R., Wilson, R. S., Kamenetsky, J. M., Barnes, L. L., Bienias, J. L., & Bennett, D. A. (2009). Social engagement and cognitive function in old age. *Exp Aging Res, 35*(1), 45-60. doi:10.1080/03610730802545028

Larrabee Sonderlund, A., Thilsing, T., & Sondergaard, J. (2019). Should social disconnectedness be included in primary-care screening for cardiometabolic disease? A systematic review

of the relationship between everyday stress, social connectedness, and allostatic load. *PLoS One, 14*(12), e0226717. doi:10.1371/journal.pone.0226717

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., Markus, H. S., & CoStream Consortium, o. b. o. t. I. G. o. A. s. P. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ, 359*, j5375. doi:10.1136/bmj.j5375

Larsson, S. C., & Wolk, A. (2018). The Role of Lifestyle Factors and Sleep Duration for Late-Onset Dementia: A Cohort Study. *J Alzheimers Dis, 66*(2), 579-586. doi:10.3233/JAD-180529

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol, 58*(3), 498-504. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11255456

Lautenschlager, N. T., Cox, K., & Kurz, A. F. (2010). Physical activity and mild cognitive impairment and Alzheimer's disease. *Curr Neurol Neurosci Rep, 10*(5), 352-358. doi:10.1007/s11910-010-0121-7

Li, Y., Pan, A., Wang, D. D., Liu, X., Dhana, K., Franco, O. H., . . . Hu, F. B. (2018). Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. *Circulation, 138*(4), 345-355. doi:10.1161/circulationaha.117.032047

Liang, K. Y., Mintun, M. A., Fagan, A. M., Goate, A. M., Bugg, J. M., Holtzman, D. M., . . . Head, D. (2010). Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol, 68*(3), 311-318. doi:10.1002/ana.22096

Lim, A. S., Kowgier, M., Yu, L., Buchman, A. S., & Bennett, D. A. (2013). Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep, 36*(7), 1027-1032. doi:10.5665/sleep.2802

Lim, A. S., Yu, L., Costa, M. D., Buchman, A. S., Bennett, D. A., Leurgans, S. E., & Saper, C. B. (2011). Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. *Sleep, 34*(11), 1569-1581. doi:10.5665/sleep.1400

Lim, A. S., Yu, L., Costa, M. D., Leurgans, S. E., Buchman, A. S., Bennett, D. A., & Saper, C. B. (2012). Increased fragmentation of rest-activity patterns is associated with a characteristic pattern of cognitive impairment in older individuals. *Sleep, 35*(5), 633-640B. doi:10.5665/sleep.1820

Lim, A. S., Yu, L., Kowgier, M., Schneider, J. A., Buchman, A. S., & Bennett, D. A. (2013). Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol, 70*(12), 1544-1551. doi:10.1001/jamaneurol.2013.4215

Liu, Y. (2016). Prevalence of healthy sleep duration among adults—United States, 2014. *MMWR. Morbidity and mortality weekly report, 65*.

Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M., & Handy, T. C. (2012). Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiol Aging, 33*(8), 1690-1698. doi:10.1016/j.neurobiolaging.2011.05.010

Lobo, E., Dufouil, C., Marcos, G., Quetglas, B., Saz, P., Guallar, E., . . . Workgroup, Z. (2010). Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? *Am J Epidemiol, 172*(6), 708-716. doi:10.1093/aje/kwq187

Lopez-Arrieta, J. M., Rodriguez, J. L., & Sanz, F. (2000). Nicotine for Alzheimer's disease. *Cochrane Database Syst Rev*(2), CD001749. doi:10.1002/14651858.CD001749

Loughrey, D. G., Lavecchia, S., Brennan, S., Lawlor, B. A., & Kelly, M. E. (2017). The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. *Adv Nutr, 8*(4), 571-586. doi:10.3945/an.117.015495

Lourida, I., Hannon, E., Littlejohns, T. J., Langa, K. M., Hypponen, E., Kuzma, E., & Llewellyn, D. J. (2019). Association of Lifestyle and Genetic Risk With Incidence of Dementia. *JAMA*. doi:10.1001/jama.2019.9879

Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I. A., Ukoumunne, O. C., & Llewellyn, D. J. (2013). Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology, 24*(4), 479-489. doi:10.1097/EDE.0b013e3182944410

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA, 288*(12), 1475-1483. doi:10.1001/jama.288.12.1475

MacNeil-Vroomen, J., Schulz, R., Doyle, M., Murphy, T. E., Ives, D. G., & Monin, J. K. (2018). Time-varying social support and time to death in the cardiovascular health study. *Health Psychol, 37*(11), 1000-1005. doi:10.1037/hea0000660

Macpherson, H., Teo, W. P., Schneider, L. A., & Smith, A. E. (2017). A Life-Long Approach to Physical Activity for Brain Health. *Front Aging Neurosci, 9*, 147. doi:10.3389/fnagi.2017.00147

Mamalaki, E., Anastasiou, C. A., Kosmidis, M. H., Dardiotis, E., Hadjigeorgiou, G. M., Sakka, P., . . . Yannakoulia, M. (2020). Social life characteristics in relation to adherence to the Mediterranean diet in older adults: findings from the Hellenic Longitudinal Investigation

of Aging and Diet (HELIAD) study. *Public Health Nutr*, *23*(3), 439-445. doi:10.1017/S1368980019002350

Mantantzis, K., Maylor, E. A., & Schlaghecken, F. (2018). Gain without pain: Glucose promotes cognitive engagement and protects positive affect in older adults. *Psychol Aging*, *33*(5), 789-797. doi:10.1037/pag0000270

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A. A. M., Bialecka-Debek, A., . . . Franceschi, C. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. *Front Physiol*, *9*, 349. doi:10.3389/fphys.2018.00349

Martinez-Lapiscina, E. H., Clavero, P., Toledo, E., Estruch, R., Salas-Salvado, J., San Julian, B., . . . Martinez-Gonzalez, M. A. (2013). Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry*, *84*(12), 1318-1325. doi:10.1136/jnnp-2012-304792

Martins, C., Morgan, L., & Truby, H. (2008). A review of the effects of exercise on appetite regulation: an obesity perspective. *Int J Obes (Lond)*, *32*(9), 1337-1347. doi:10.1038/ijo.2008.98

Mastorakou, D., Rabaeus, M., Salen, P., Pounis, G., & de Lorgeril, M. (2019). Chapter 9 - Mediterranean Diet: A Health-Protective Dietary Pattern for Modern Times. In G. Pounis (Ed.), *Analysis in Nutrition Research* (pp. 233-258): Academic Press.

Maust, D. T., Solway, E., Langa, K. M., Kullgren, J. T., Kirch, M., Singer, D. C., & Malani, P. (2019). Perception of Dementia Risk and Preventive Actions Among US Adults Aged 50 to 64 Years. *JAMA Neurol*. doi:10.1001/jamaneurol.2019.3946

Mawditt, C., Sacker, A., Britton, A., Kelly, Y., & Cable, N. (2016). The clustering of health-related behaviours in a British population sample: Testing for cohort differences. *Prev Med, 88*, 95-107. doi:10.1016/j.ypmed.2016.03.003

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology, 24*(1), 9-34. doi:10.1037/a0017336

McEvoy, C. T., Guyer, H., Langa, K. M., & Yaffe, K. (2017). Neuroprotective Diets Are Associated with Better Cognitive Function: The Health and Retirement Study. *J Am Geriatr Soc, 65*(8), 1857-1862. doi:10.1111/jgs.14922

McHugh Power, J. E., Steptoe, A., Kee, F., & Lawlor, B. A. (2019). Loneliness and social engagement in older adults: A bivariate dual change score analysis. *Psychol Aging, 34*(1), 152-162. doi:10.1037/pag0000287

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-944. doi:10.1212/wnl.34.7.939

Mehl-Madrona, L., & Mainguy, B. (2017). Collaborative Management of Neurocognitive Disorders in Primary Care: Explorations of an Attempt at Culture Change. *Perm J, 21*. doi:10.7812/TPP/16-027

Mehta, D., Jackson, R., Paul, G., Shi, J., & Sabbagh, M. (2017). Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert opinion on investigational drugs, 26*(6), 735-739. doi:10.1080/13543784.2017.1323868

Memel, M., Bourassa, K., Woolverton, C., & Sbarra, D. A. (2016). Body Mass and Physical Activity Uniquely Predict Change in Cognition for Aging Adults. *Ann Behav Med, 50*(3), 397-408. doi:10.1007/s12160-015-9768-2

Mendes de Leon, C. F., Glass, T. A., & Berkman, L. F. (2003). Social engagement and disability in a community population of older adults: the New Haven EPESE. *Am J Epidemiol, 157*(7), 633-642. doi:10.1093/aje/kwg028

Meng, X.-l., Rosenthal, R., & Rubin, D. B. (1992). Comparing correlated correlation coefficients. *Psychological Bulletin, 111*(1), 172-175. doi:10.1037/0033-2909.111.1.172

Merrill, D. A., Siddarth, P., Raji, C. A., Emerson, N. D., Rueda, F., Ercoli, L. M., . . . Small, G. W. (2016). Modifiable Risk Factors and Brain Positron Emission Tomography Measures of Amyloid and Tau in Nondemented Adults with Memory Complaints. *Am J Geriatr Psychiatry, 24*(9), 729-737. doi:10.1016/j.jagp.2016.05.007

Moreno-Smith, M., Lutgendorf, S. K., & Sood, A. K. (2010). Impact of stress on cancer metastasis. *Future Oncol, 6*(12), 1863-1881. doi:10.2217/fon.10.142

Morrill, S. J., & Gibas, K. J. (2019). Ketogenic diet rescues cognition in ApoE4+ patient with mild Alzheimer's disease: A case study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13*(2), 1187-1191.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., . . . Clark, C. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology, 39*(9), 1159-1165. doi:10.1212/wnl.39.9.1159

Morris, M. C. (2016). Nutrition and risk of dementia: overview and methodological issues. *Ann N Y Acad Sci, 1367*(1), 31-37. doi:10.1111/nyas.13047

Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Barnes, L. L., Bennett, D. A., & Aggarwal, N. T. (2015). MIND diet slows cognitive decline with aging. *Alzheimers Dement, 11*(9), 1015-1022. doi:10.1016/j.jalz.2015.04.011

Morris, M. C., Wang, Y., Barnes, L. L., Bennett, D. A., Dawson-Hughes, B., & Booth, S. L. (2018). Nutrients and bioactives in green leafy vegetables and cognitive decline: Prospective study. *Neurology, 90*(3), e214-e222. doi:10.1212/WNL.0000000000004815

Mosconi, L., & McHugh, P. F. (2015). Let Food Be Thy Medicine: Diet, Nutrition, and Biomarkers' Risk of Alzheimer's Disease. *Curr Nutr Rep, 4*(2), 126-135. doi:10.1007/s13668-014-0111-5

Mosconi, L., Mistur, R., Switalski, R., Tsui, W. H., Glodzik, L., Li, Y., . . . de Leon, M. J. (2009). FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 36*(5), 811-822. doi:10.1007/s00259-008-1039-z

Motl, R. W., & Sandroff, B. M. (2015). Benefits of Exercise Training in Multiple Sclerosis. *Current Neurology and Neuroscience Reports, 15*(9), 62. doi:10.1007/s11910-015-0585-6

Muller, S., Preische, O., Sohrabi, H. R., Graber, S., Jucker, M., Ringman, J. M., . . . Dominantly Inherited Alzheimer, N. (2018). Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. *Alzheimers Dement, 14*(11), 1427-1437. doi:10.1016/j.jalz.2018.06.3059

Munoz, E., Sliwinski, M. J., Scott, S. B., & Hofer, S. (2015). Global perceived stress predicts cognitive change among older adults. *Psychol Aging, 30*(3), 487-499. doi:10.1037/pag0000036

Naderi, A., Shaabani, F., Esmaeili, A., Salman, Z., Borella, E., & Degens, H. (2019). Effects of low and moderate acute resistance exercise on executive function in community-living older adults. *Sport, Exercise, and Performance Psychology, 8*(1), 106-122. doi:10.1037/spy0000135

Nagamatsu, L. S., Handy, T. C., Hsu, C. L., Voss, M., & Liu-Ambrose, T. (2012). Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch Intern Med, 172*(8), 666-668. doi:10.1001/archinternmed.2012.379

Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., . . . Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet, 385*(9984), 2255-2263. doi:10.1016/S0140-6736(15)60461-5

Nguyen, J. C., Killcross, A. S., & Jenkins, T. A. (2014). Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci, 8*, 375. doi:10.3389/fnins.2014.00375

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *British Journal of Sports Medicine, 52*(3), 154-160. doi:10.1136/bjsports-2016-096587

Norton, M. C., Dew, J., Smith, H., Fauth, E., Piercy, K. W., Breitner, J. C., . . . Welsh-Bohmer, K. (2012). Lifestyle behavior pattern is associated with different levels of risk for

incident dementia and Alzheimer's disease: the Cache County study. *J Am Geriatr Soc, 60*(3), 405-412. doi:10.1111/j.1532-5415.2011.03860.x

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol, 13*(8), 788-794. doi:10.1016/S1474-4422(14)70136-X

Ota, M., Matsuo, J., Ishida, I., Takano, H., Yokoi, Y., Hori, H., . . . Kunugi, H. (2019). Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. *Neurosci Lett, 690*, 232-236. doi:10.1016/j.neulet.2018.10.048

PASS. (2019). Power Analysis and Sample Size Software Kaysville, Utah, USA: NCSS, LLC. Retrieved from ncss.com/software/pass

Peavy, G. M., Jacobson, M. W., Salmon, D. P., Gamst, A. C., Patterson, T. L., Goldman, S., . . . Galasko, D. (2012). The influence of chronic stress on dementia-related diagnostic change in older adults. *Alzheimer Dis Assoc Disord, 26*(3), 260-266. doi:10.1097/WAD.0b013e3182389a9c

Peavy, G. M., Salmon, D. P., Jacobson, M. W., Hervey, A., Gamst, A. C., Wolfson, T., . . . Galasko, D. (2009). Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry, 166*(12), 1384-1391. doi:10.1176/appi.ajp.2009.09040461

Peterman, M. (1925). The ketogenic diet in epilepsy. *Journal of the American Medical Association, 84*(26), 1979-1983.

Peters, R., Peters, J., Warner, J., Beckett, N., & Bulpitt, C. (2008). Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing, 37*(5), 505-512. doi:10.1093/ageing/afn095

Petersen, R. C., Lopez, O., Armstrong, M. J., Getchius, T. S. D., Ganguli, M., Gloss, D., . . . Rae-Grant, A. (2018). Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology, 90*(3), 126-135. doi:10.1212/WNL.0000000000004826

Pistollato, F., Ohayon, E. L., Lam, A., Langley, G. R., Novak, T. J., Pamies, D., . . . Chandrasekera, P. C. (2016). Alzheimer disease research in the 21st century: past and current failures, new perspectives and funding priorities. *Oncotarget, 7*(26), 38999-39016. doi:10.18632/oncotarget.9175

Potvin, O., Lorrain, D., Forget, H., Dube, M., Grenier, S., Preville, M., & Hudon, C. (2012). Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep, 35*(4), 491-499. doi:10.5665/sleep.1732

Prinz, P. N., Peskind, E. R., Vitaliano, P. P., Raskind, M. A., Eisdorfer, C., Zemcuznikov, N., & Gerber, C. J. (1982). Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *J Am Geriatr Soc, 30*(2), 86-93. doi:10.1111/j.1532-5415.1982.tb01279.x

Radak, Z., Hart, N., Sarga, L., Koltai, E., Atalay, M., Ohno, H., & Boldogh, I. (2010). Exercise plays a preventive role against Alzheimer's disease. *J Alzheimers Dis, 20*(3), 777-783. doi:10.3233/jad-2010-091531

Rakesh, G., Szabo, S. T., Alexopoulos, G. S., & Zannas, A. S. (2017). Strategies for dementia prevention: latest evidence and implications. *Ther Adv Chronic Dis, 8*(8-9), 121-136. doi:10.1177/2040622317712442

Rao, A. K., Chou, A., Bursley, B., Smulofsky, J., & Jezequel, J. (2014). Systematic review of the effects of exercise on activities of daily living in people with Alzheimer's disease. *Am J Occup Ther, 68*(1), 50-56. doi:10.5014/ajot.2014.009035

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological reviews, 93*(2), 681-766. doi:10.1152/physrev.00032.2012

Raven, J. (1992). Court JH, Raven J. Standard Progressive Matrices—1992 edition. Raven manual: section 3. In: Oxford: Oxford Psychologists Press.

Rege, S. D., Geetha, T., Broderick, T. L., & Babu, J. R. (2017). Can Diet and Physical Activity Limit Alzheimer's Disease Risk? *Curr Alzheimer Res, 14*(1), 76-93. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26971938

Reger, M. A., Henderson, S. T., Hale, C., Cholerton, B., Baker, L. D., Watson, G. S., . . . Craft, S. (2004). Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging, 25*(3), 311-314. doi:10.1016/S0197-4580(03)00087-3

Rexroth, D. F., Tennstedt, S. L., Jones, R. N., Guey, L. T., Rebok, G. W., Marsiske, M. M., . . . Unverzagt, F. W. (2013). Relationship of demographic and health factors to cognition in older adults in the ACTIVE study. *J Aging Health, 25*(8 Suppl), 128S-146S. doi:10.1177/0898264313498415

Rogers, J., Webster, S., Lue, L. F., Brachova, L., Civin, W. H., Emmerling, M., . . . McGeer, P. (1996). Inflammation and Alzheimer's disease pathogenesis. *Neurobiol Aging, 17*(5), 681-686. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8892340

Rogers, R. L., Meyer, J. S., & Mortel, K. F. (1990). After reaching retirement age physical activity sustains cerebral perfusion and cognition. *Journal of the American Geriatrics Society, 38*(2), 123-128.

Rolland, Y., Pillard, F., Klapouszczak, A., Reynish, E., Thomas, D., Andrieu, S., . . . Vellas, B. (2007). Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. *J Am Geriatr Soc, 55*(2), 158-165. doi:10.1111/j.1532-5415.2007.01035.x

Rosenberg, A., Coley, N., Soulier, A., Kulmala, J., Soininen, H., Andrieu, S., . . . groups, H. (2020). Experiences of dementia and attitude towards prevention: a qualitative study among older adults participating in a prevention trial. *BMC Geriatr, 20*(1), 99. doi:10.1186/s12877-020-1493-4

Rosenberg, A., Mangialasche, F., Ngandu, T., Solomon, A., & Kivipelto, M. (2020). Multidomain Interventions to Prevent Cognitive Impairment, Alzheimer's Disease, and Dementia: From FINGER to World-Wide FINGERS. *J Prev Alzheimers Dis, 7*(1), 29-36. doi:10.14283/jpad.2019.41

Rosnick, C. B., Small, B. J., McEvoy, C. L., Borenstein, A. R., & Mortimer, J. A. (2007). Negative life events and cognitive performance in a population of older adults. *J Aging Health, 19*(4), 612-629. doi:10.1177/0898264307300975

Saez de Asteasu, M. L., Martinez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, A., & Izquierdo, M. (2017). Role of physical exercise on cognitive function in healthy older adults: A systematic review of randomized clinical trials. *Ageing Res Rev, 37*, 117-134. doi:10.1016/j.arr.2017.05.007

Samieri, C., Okereke, O. I., E, E. D., & Grodstein, F. (2013). Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. *J Nutr, 143*(4), 493-499. doi:10.3945/jn.112.169896

Sapolsky, R. M. (1992). Endocrinology of the stress-response. In J. B. Becker, S. M. Breedlove, & D. Crews (Eds.), *Behavioral endocrinology* (2 ed., pp. 409-450). Cambridge, Mass.: MIT Press.

Sauter, J., Widmer, E., Baeriswyl, M., Ballhausen, N., Vallet, F., Fagot, D., . . . Ihle, A. (2020). Interactional effects between relational and cognitive reserves on decline in executive functioning. *J Gerontol B Psychol Sci Soc Sci*. doi:10.1093/geronb/gbaa054

Sauter, J., Widmer, E., Ihle, A., & Kliegel, M. (2019). The association of leisure activities in middle adulthood with cognitive performance in old age: Social capital mediates cognitive reserve effects. *Psychology & Neuroscience, 12*(2), 236-246. doi:10.1037/pne0000146

Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., & Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA, 302*(6), 627-637. doi:10.1001/jama.2009.1144

Scarmeas, N., Stern, Y., Mayeux, R., Manly, J. J., Schupf, N., & Luchsinger, J. A. (2009). Mediterranean diet and mild cognitive impairment. *Arch Neurol, 66*(2), 216-225. doi:10.1001/archneurol.2008.536

Scarmeas, N., Stern, Y., Tang, M. X., Mayeux, R., & Luchsinger, J. A. (2006). Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol, 59*(6), 912-921. doi:10.1002/ana.20854

Schelke, M. W., Hackett, K., Chen, J. L., Shih, C., Shum, J., Montgomery, M. E., . . . Isaacson, R. S. (2016). Nutritional interventions for Alzheimer's prevention: a clinical precision medicine approach. *Ann N Y Acad Sci, 1367*(1), 50-56. doi:10.1111/nyas.13070

Schmeidler, J., Mastrogiacomo, C. N., Beeri, M. S., Rosendorff, C., & Silverman, J. M. (2019). Distinct age-related associations for body mass index and cognition in cognitively healthy very old veterans. *Int Psychogeriatr, 31*(6), 895-899. doi:10.1017/S1041610218001412

Schultz, S. A., Boots, E. A., Darst, B. F., Zetterberg, H., Blennow, K., Edwards, D. F., . . . Okonkwo, O. C. (2017). Cardiorespiratory fitness alters the influence of a polygenic risk score on biomarkers of AD. *Neurology, 88*(17), 1650-1658. doi:10.1212/WNL.0000000000003862

Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. *Perspect Psychol Sci, 10*(1), 97-137. doi:10.1177/1745691614556680

Serra-Majem, L., Roman, B., & Estruch, R. (2006). Scientific evidence of interventions using the Mediterranean diet: a systematic review. *Nutrition reviews, 64*(suppl_1), S27-S47.

Services, U. D. o. H. a. H. (2006). *Your Guide to Lowering Your Blood Pressure with DASH*. Retrieved from http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm

The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General, (2014).

Services, U. S. D. o. H. a. H. (2018). *Physical Activity Guidelines for Americans*. Retrieved from

Shakersain, B., Rizzuto, D., Wang, H. X., Faxen-Irving, G., Prinelli, F., Fratiglioni, L., & Xu, W. (2018). An Active Lifestyle Reinforces the Effect of a Healthy Diet on Cognitive Function: A Population-Based Longitudinal Study. *Nutrients, 10*(9). doi:10.3390/nu10091297

Shatenstein, B., Kergoat, M. J., & Nadon, S. (2001). Weight change, nutritional risk and its determinants among cognitively intact and demented elderly Canadians. *Can J Public Health, 92*(2), 143-149. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11338154

Shokri-Kojori, E., Wang, G. J., Wiers, C. E., Demiral, S. B., Guo, M., Kim, S. W., . . . Volkow, N. D. (2018). beta-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A, 115*(17), 4483-4488. doi:10.1073/pnas.1721694115

Sierra-Fonseca, J. A., & Gosselink, K. L. (2018). Tauopathy and neurodegeneration: A role for stress. *Neurobiol Stress, 9,* 105-112. doi:10.1016/j.ynstr.2018.08.009

Sims-Gould, J., Franke, T., Lusina-Furst, S., & McKay, H. A. (2020). Community health promotion programs for older adults: What helps and hinders implementation. *Health Sci Rep, 3*(1), e144. doi:10.1002/hsr2.144

Smith, A. (1984). *Symbol digit modalities test-revised*: Western Psychological Services Los Angeles, CA.

Smith, B. M., Yao, X., Chen, K. S., & Kirby, E. D. (2018). A Larger Social Network Enhances Novel Object Location Memory and Reduces Hippocampal Microgliosis in Aged Mice. *Front Aging Neurosci, 10,* 142. doi:10.3389/fnagi.2018.00142

Soderholm, J. D., & Perdue, M. H. (2001). Stress and gastrointestinal tract. II. Stress and intestinal barrier function. *Am J Physiol Gastrointest Liver Physiol, 280*(1), G7-G13. doi:10.1152/ajpgi.2001.280.1.G7

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med, 269*(1), 107-117. doi:10.1111/j.1365-2796.2010.02281.x

Solomon, A., Turunen, H., Ngandu, T., Peltonen, M., Levalahti, E., Helisalmi, S., . . . Kivipelto, M. (2018). Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention: A Subgroup Analysis of a Randomized Clinical Trial. *JAMA Neurol, 75*(4), 462-470. doi:10.1001/jamaneurol.2017.4365

Sommerlad, A., Ruegger, J., Singh-Manoux, A., Lewis, G., & Livingston, G. (2018). Marriage and risk of dementia: systematic review and meta-analysis of observational studies. *J Neurol Neurosurg Psychiatry, 89*(3), 231-238. doi:10.1136/jnnp-2017-316274

Spencer, C. A., Jamrozik, K., Norman, P. E., & Lawrence-Brown, M. (2005). A simple lifestyle score predicts survival in healthy elderly men. *Prev Med, 40*(6), 712-717. doi:10.1016/j.ypmed.2004.09.012

Spira, A. P., Chen-Edinboro, L. P., Wu, M. N., & Yaffe, K. (2014). Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry, 27*(6), 478-483. doi:10.1097/YCO.0000000000000106

Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., . . . Resnick, S. M. (2013). Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol, 70*(12), 1537-1543. doi:10.1001/jamaneurol.2013.4258

Stacey, C., Kozma, A., & Stones, M. (1985). Simple cognitive and behavioural changes resulting from improved physical fitness in persons over 50 years of age. *Canadian Journal on Aging/La Revue canadienne du vieillissement, 4*(2), 67-74.

Stampfer, M. J., Kang, J. H., Chen, J., Cherry, R., & Grodstein, F. (2005). Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med, 352*(3), 245-253. doi:10.1056/NEJMoa041152

Stein, J. Y., Levin, Y., Lahav, Y., Uziel, O., Abumock, H., & Solomon, Z. (2018). Perceived social support, loneliness, and later life telomere length following wartime captivity. *Health Psychol, 37*(11), 1067-1076. doi:10.1037/hea0000669

Sterniczuk, R., Theou, O., Rusak, B., & Rockwood, K. (2013). Sleep disturbance is associated with incident dementia and mortality. *Curr Alzheimer Res, 10*(7), 767-775.

Sundstrom, A., Adolfsson, A. N., Nordin, M., & Adolfsson, R. (2020). Loneliness Increases the Risk of All-Cause Dementia and Alzheimer's Disease. *J Gerontol B Psychol Sci Soc Sci, 75*(5), 919-926. doi:10.1093/geronb/gbz139

Suri, S., Heise, V., Trachtenberg, A. J., & Mackay, C. E. (2013). The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE varepsilon2. *Neurosci Biobehav Rev, 37*(10 Pt 2), 2878-2886. doi:10.1016/j.neubiorev.2013.10.010

Tangney, C. C., Kwasny, M. J., Li, H., Wilson, R. S., Evans, D. A., & Morris, M. C. (2011). Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. *Am J Clin Nutr, 93*(3), 601-607. doi:10.3945/ajcn.110.007369

Tangney, C. C., Li, H., Wang, Y., Barnes, L., Schneider, J. A., Bennett, D. A., & Morris, M. C. (2014). Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology, 83*(16), 1410-1416. doi:10.1212/WNL.0000000000000884

Topiwala, A., Allan, C. L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C., . . . Ebmeier, K. P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ, 357*, j2353. doi:10.1136/bmj.j2353

Topiwala, A., & Ebmeier, K. P. (2018). Effects of drinking on late-life brain and cognition. *Evid Based Ment Health, 21*(1), 12-15. doi:10.1136/eb-2017-102820

Trenerry, M. R., Crosson, B., DeBoe, J., & Leber, W. (1989). Stroop neuropsychological screening test. *Odessa, FL: Psychological Assessment Resources*.

Tsapanou, A., Gu, Y., Manly, J., Schupf, N., Tang, M. X., Zimmerman, M., . . . Stern, Y. (2015). Daytime Sleepiness and Sleep Inadequacy as Risk Factors for Dementia. *Dement Geriatr Cogn Dis Extra, 5*(2), 286-295. doi:10.1159/000431311

Tschanz, J. T., Pfister, R., Wanzek, J., Corcoran, C., Smith, K., Tschanz, B. T., . . . Norton, M. C. (2013). Stressful life events and cognitive decline in late life: moderation by education and age. The Cache County Study. *Int J Geriatr Psychiatry, 28*(8), 821-830. doi:10.1002/gps.3888

Turner, A. D., James, B. D., Capuano, A. W., Aggarwal, N. T., & Barnes, L. L. (2017). Perceived Stress and Cognitive Decline in Different Cognitive Domains in a Cohort of Older African Americans. *Am J Geriatr Psychiatry, 25*(1), 25-34. doi:10.1016/j.jagp.2016.10.003

Tworoger, S. S., Lee, S., Schernhammer, E. S., & Grodstein, F. (2006). The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older

women. *Alzheimer Dis Assoc Disord, 20*(1), 41-48. doi:10.1097/01.wad.0000201850.52707.80

van de Rest, O., Berendsen, A. A., Haveman-Nies, A., & de Groot, L. C. (2015). Dietary patterns, cognitive decline, and dementia: a systematic review. *Adv Nutr, 6*(2), 154-168. doi:10.3945/an.114.007617

Visser, M., Wijnhoven, H. A. H., Comijs, H. C., Thomese, F., Twisk, J. W. R., & Deeg, D. J. H. (2019). A Healthy Lifestyle in Old Age and Prospective Change in Four Domains of Functioning. *J Aging Health, 31*(7), 1297-1314. doi:10.1177/0898264318774430

Watson, N. F., Badr, M. S., Belenky, G., Bliwise, D. L., Buxton, O. M., Buysse, D., . . . Tasali, E. (2015). Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep, 38*(6), 843-844. doi:10.5665/sleep.4716

Watt, R. G., Heilmann, A., Sabbah, W., Newton, T., Chandola, T., Aida, J., . . . Tsakos, G. (2014). Social relationships and health related behaviors among older US adults. *BMC Public Health, 14*, 533. doi:10.1186/1471-2458-14-533

Wechsler, D. (1987). *WMS-R : Wechsler Memory Scale--Revised : manual*. San Antonio: Psychological Corp. : Harcourt Brace Jovanovich.

Weng, P. H., Chen, J. H., Chiou, J. M., Tu, Y. K., Chen, T. F., Chiu, M. J., . . . Chen, Y. C. (2018). The effect of lifestyle on late-life cognitive change under different socioeconomic status. *PLoS One, 13*(6), e0197676. doi:10.1371/journal.pone.0197676

Wesselman, L. M. P., van Lent, D. M., Schroder, A., van de Rest, O., Peters, O., Menne, F., . . . Wagner, M. (2020). Dietary patterns are related to cognitive functioning in elderly

enriched with individuals at increased risk for Alzheimer's disease. *Eur J Nutr*. doi:10.1007/s00394-020-02257-6

Westwood, A. J., Beiser, A., Jain, N., Himali, J. J., DeCarli, C., Auerbach, S. H., . . . Seshadri, S. (2017). Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. *Neurology, 88*(12), 1172-1179. doi:10.1212/WNL.0000000000003732

Wheelock, M. D., Rangaprakash, D., Harnett, N. G., Wood, K. H., Orem, T. R., Mrug, S., . . . Knight, D. C. (2018). Psychosocial stress reactivity is associated with decreased whole-brain network efficiency and increased amygdala centrality. *Behav Neurosci, 132*(6), 561-572. doi:10.1037/bne0000276

White, H. (1998). Weight change in Alzheimer's disease. *J Nutr Health Aging, 2*(2), 110-112. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10993578

Wilson, R., Barnes, L., & Bennett, D. (2003). Assessment of lifetime participation in cognitively stimulating activities. *J Clin Exp Neuropsychol, 25*(5), 634-642. doi:10.1076/jcen.25.5.634.14572

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., & Bennett, D. A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging, 17*(2), 179-193. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12061405

Wilson, R. S., Boyle, P. A., James, B. D., Leurgans, S. E., Buchman, A. S., & Bennett, D. A. (2015). Negative social interactions and risk of mild cognitive impairment in old age. *Neuropsychology, 29*(4), 561-570. doi:10.1037/neu0000154

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., . . . Bennett, D. A. (2007). Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry, 64*(2), 234-240. doi:10.1001/archpsyc.64.2.234

Wilson, R. S., Scherr, P. A., Hoganson, G., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2005). Early life socioeconomic status and late life risk of Alzheimer's disease. *Neuroepidemiology, 25*(1), 8-14. doi:10.1159/000085307

Wlodarek, D. (2019). Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). *Nutrients, 11*(1). doi:10.3390/nu11010169

Wolf-Klein, G. P., & Silverstone, F. A. (1994). Weight loss in Alzheimer's disease: an international review of the literature. *Int Psychogeriatr, 6*(2), 135-142. doi:10.1017/s1041610294001705

Wright, R. S., Gerassimakis, C., Bygrave, D., & Waldstein, S. R. (2017). Dietary Factors and Cognitive Function in Poor Urban Settings. *Curr Nutr Rep, 6*(1), 32-40. doi:10.1007/s13668-017-0186-x

Wu, L., & Sun, D. (2017). Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. *Sci Rep, 7*, 41317. doi:10.1038/srep41317

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377. doi:10.1126/science.1241224

Xu, W., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., . . . Yu, J. T. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 86*(12), 1299-1306. doi:10.1136/jnnp-2015-310548

Xu, W., Wang, H. F., Wan, Y., Tan, C. C., Yu, J. T., & Tan, L. (2017). Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. *BMJ Open, 7*(10), e014706. doi:10.1136/bmjopen-2016-014706

Yaffe, K., Lindquist, K., Penninx, B. W., Simonsick, E. M., Pahor, M., Kritchevsky, S., . . . Harris, T. (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology, 61*(1), 76-80. doi:10.1212/01.wnl.0000073620.42047.d7

Yannakoulia, M., Kontogianni, M., & Scarmeas, N. (2015). Cognitive health and Mediterranean diet: just diet or lifestyle pattern? *Ageing Res Rev, 20*, 74-78. doi:10.1016/j.arr.2014.10.003

Zamroziewicz, M. K., & Barbey, A. K. (2016). Nutritional Cognitive Neuroscience: Innovations for Healthy Brain Aging. *Front Neurosci, 10*, 240. doi:10.3389/fnins.2016.00240

Zelinski, E. M., & Gilewski, M. J. (2003). Effects of demographic and health variables on Rasch scaled cognitive scores. *J Aging Health, 15*(3), 435-464. doi:10.1177/0898264303253499