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Relationship of Nutritional Factors to Cognitive Decline in the Progression of Dementia: The Cache County Dementia Progression Study

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RELATIONSHIP OF NUTRITIONAL FACTORS TO COGNITIVE DECLINE IN THE PROGRESSION OF DEMENTIA: THE CACHE COUNTY DEMENTIA PROGRESSION STUDY

by

Chelsea Sanders

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ABSTRACT

Relationship of Nutritional Factors to Cognitive Decline in the Progression of Dementia: The Cache County Dementia Progression Study

by

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Previous studies have found nutritional status to predict better functional and cognitive ability in dementia. The current study investigated the relationship between nutritional status and progression of neuropsychological impairment in a U.S. sample of persons with dementia. Participants were studied for up to 6 years in the population-based Cache County, UT, study. Baseline sample included 240 persons with dementia (71.3% Alzheimer's disease, 52.1% female). Mean (*SD*) age and dementia duration at baseline was 85.6 (5.2) and 3.4 (1.9) years, respectively. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery and Boston Naming Test (30-item) were administered annually. Nutritional status was assessed using a modified Mini Nutritional Assessment (mMNA). Components of nutritional status were chosen for further investigation (dietary intake and BMI). Linear mixed effects models examined change in nutritional status and food consumption over time as well as the association

between mMNA and its components (time-varying) with each neuropsychological measure and rate of decline over time. The following covariates were tested as appropriate: dementia type, gender, age of dementia onset and duration (at baseline), education, neuropsychiatric symptoms, caregiver coresidence, place of residence, overall health, and dementia severity.

mMNA scores decreased by .22 pts/year ($p = .006$), though this was confounded by dementia severity ($\beta = -.12$, $p = .108$). Consumption of carbohydrates ($\beta = -.09$), protein ($\beta = -.07$) and fruit/vegetables ($\beta = -.08$) also declined over time, all $p < .05$). Better nutritional status was associated with better neuropsychological test scores across all visits in verbal learning ($\beta = .23$), praxis drawing ($\beta = .23$), praxis memory ($\beta = .08$), verbal fluency ($\beta = .34$) and confrontation naming ($\beta = .31$), while mMNA predicted *rate* of decline in verbal recognition memory ($\beta = .13$); all $p < .001$, with the inclusion of covariates. Higher protein intake was associated with worse verbal learning, while higher BMI predicted better scores on all neuropsychological tests except for confrontation naming. The results emphasize the importance of nutritional status in dementia and raises the possibility of nutritional interventions that may improve patient outcomes.

(106 pages)

PUBLIC ABSTRACT

Relationship of Nutritional Factors to Cognitive Decline in the Progression of Dementia: The Cache County Dementia Progression Study

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Utah State University, 2015

The Cache County Memory Study at Utah State University studied longitudinal changes in memory and aging in a population-based sample of 5,092 older adults in semirural Cache County, UT. Three hundred twenty-eight participants with dementia were identified through a multi-staged screening and assessment protocol and visited semiannually for up to 8 years in the Dementia Progression Study (DPS). The current project reviews data from the first 6 years due to attrition in later years. Researchers collected information regarding the participants' demographics, health, lifestyle (nutrition and physical activity), cognitive abilities and neuropsychiatric symptoms as well as their caregivers' demographics, health, and well-being. Both studies, funded by the National Institute on Aging, have allowed researchers to investigate many lifestyle and genetic factors that are associated with an increased risk and/or progression of Alzheimer's disease and other dementias.

Nutrition is an important lifestyle factor in maintaining cognitive health throughout aging. The current investigation focused primarily on the link between

nutritional factors and cognitive decline among persons with dementia. Individuals with dementia are at an increased risk for malnutrition, and those who are malnourished experience worse cognitive, functional, and neuropsychiatric symptoms. If factors such as nutritional status slow the progression of dementia, this may reduce an individual's level of dependence on others and increase the quality of life for people with dementia and their caregivers. Therefore, the current investigation examined the relationship between aspects of nutritional status and specific cognitive domains of memory, visuospatial skills, verbal expression, and executive functions in participants of the DPS. A better understanding of the impact of nutritional factors on these cognitive areas that are affected by dementia will help provide a better understanding of the overall influence of nutrition on dementia progression and potentially lead to more successful nutrition-related dementia interventions.

DEDICATION

A lot can happen in 3 years. One journey begins in pursuit of knowledge as another concludes in the deterioration of such. In this case, two earthly voyages were called to a close: one in slow agonizing form while the other in a heartbreaking halt but both consequences of neural degeneration from dementia. During the defense of this thesis, I reflected on the experiences of two family members who were intimately acquainted with its topic. In loving memory, I dedicate this work to my uncle, James Thomas Sanders, Jr. (May 11, 1946-April 4, 2015), and grandmother, Lorraine A. Robinson (January 29, 1930-February 7, 2015).

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Chelsea Sanders

CONTENTS

Page

LIST OF TABLES

Table Page

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Dementia is characterized by impairments in a person's memory, cognitive ability, and behavior that significantly decrease the person's previous level of social and occupational functioning (American Psychiatric Association [APA], 2000). The syndrome affects tens of millions of people worldwide and continues to increase in prevalence. Current estimates indicate that one in three older adults die with some form of dementia (Alzheimer's Association, 2013). In fact, approximately 36.5 million people around the world lived with dementia in 2010, and based on the current rate of growth, this number is expected to double every 20 years to reach 115.4 million by 2050 (Prince et al., 2013). This phenomenon is partly due to population growth and increased life expectancy. In the U.S., members of the "Baby Boomer" generation ages in a period of significant medical innovation, which has greatly reduced the mortality rates of heart disease, stroke, and prostate cancer (Alzheimer's Association, 2013). Consequently, the average person is more likely to live longer and therefore, more likely to be at risk for age-related cognitive conditions such as dementia. Although the past 30 years is marked by a prolific amount of research dedicated to understanding dementia, there is still much to learn in regards to prevention and treatment strategies.

Nutrition is an important lifestyle factor for maintaining cognitive health in aging and reducing the risk for dementia (Povova et al., 2012). People with dementia who are malnourished or at risk for malnutrition experience more severe dementia symptoms (Guerin et al., 2005; Soto et al., 2008; Spaccavento, Del Prete, Craca, & Fiore, 2008;

Vellas et al., 2005). Research has also demonstrated that particular aspects of nutritional status such as diet, weight, and body mass index (BMI) throughout mid and late life are related to the development of dementia or its severity after onset (Albanese et al., 2013; M. C. Morris, 2012; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). However, these studies revealed little about the progression of dementia symptoms in relation to nutritional status. Furthermore, the outcomes of these studies are limited to functional, neuropsychiatric, and global cognitive measures of dementia progression and have not explored specific neuropsychological symptoms associated with dementia. In addition, it is not yet understood how nutritional status and related aspects of diet, weight, and BMI relate to the progression of dementia symptoms, specifically in neuropsychological domains of memory, executive functioning, expressive language, and visuospatial abilities.

A better understanding of the impact of nutritional status on the neuropsychological symptoms of dementia will help provide a better understanding of the overall influence of nutrition on dementia progression, which could potentially lead to more successful nutrition-related intervention strategies. Therefore, the purpose of this study is to determine the relationship between nutritional status and related aspects on the neuropsychological symptoms of dementia through a secondary data analysis of the Cache County Dementia Progression Study, a population-based study of dementia progression in Cache County, UT.

CHAPTER II

LITERATURE REVIEW

Overall Significance of Dementia

Dementia is a clinical syndrome that describes a set of symptoms common to several disorders of diverse etiology. Neurodegenerative and progressive in nature, the most common causes of dementia in late life include Alzheimer's disease (AD), vascular dementia (VaD), Lewy-Body dementia, and fronto-temporal dementia. Of these, AD is the most prevalent and commonly researched. In fact, AD is estimated to account for 75% of all dementias worldwide (Povova et al., 2012). According to the Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM IV), AD is a form of dementia characterized by impairments in memory and disturbances in at least one of the following cognitive domains: language, executive functioning, and/or visuospatial reasoning. DSM IV criteria for AD require that these impairments are gradual at onset and progressive throughout the course of the disease, causing significant handicaps in social or occupational functioning (APA, 2000). The epidemiology of AD and other dementias has broad implications both within the U.S. and across the world. In particular, loss of cognitive and functional capacities for independence early in a disease that is of long duration incurs high medical costs and caregiver burden over time. Therefore, maintenance of independence for as long as possible among patients with dementia is critical.

Current treatment options for patients diagnosed with AD and other dementias are

limited. Early pharmacological therapies were based on the "cholinergic hypothesis" which posited that AD was caused by a deficit in acetycholine production. As a result, most pharmacological treatments aim to stimulate cholingeric activity. More recent pharmacological treatments under development target amyloid-β production, a substance that in AD is abnormally deposited in several brain regions (Wierenga & Bondi, 2011). Though some pharmacological approaches have demonstrated modest effectiveness in temporarily reducing symptoms in people with mild to moderate AD, there are currently no medications that change the course or target the underlying cause of the disease (Alzheimer's Association, 2013). Since the neuropathological processes of AD and other dementias are not completely understood, prevention methods target risk factors including psychosocial and vascular factors.

Many researchers have investigated the role of environmental factors in the development of dementia, including education, physical exercise, mental activity, social engagement, and diet and nutrition (Povova et al., 2012). Of these lifestyle-related factors, nutrition is one of the broadest topics, ranging in specificity from blood levels of particular vitamins to basic anthropomorphic features such as BMI.

Nutritional Factors in Aging and Dementia

In order to gain insights on why nutrition is explored as an avenue for dementia prevention and how nutritional factors may affect the progression of dementia, it is important to consider the basic relationship between nutrition and cognition in current research. Extensive research on nutrition and aging suggests the role of specific micro-

and macronutrients in the prevention of neurodegenerative disease. Micronutrients are the trace amounts of vitamins and minerals that organisms need for the body's proper development and functioning, whereas macronutrients are required in relatively large amounts for normal organism growth and survival (fats, proteins, and carbohydrates). Research suggests that a diet balanced with the combination of antioxidants, B vitamins, and vitamin E (micronutrients), as well as polyunsaturated fats, and DHA omega 3 fatty acids (macronutrients) may be protective in preserving brain function (Engelhart et al., 2002; M. C. Morris, 2012). These nutrients are found in fruits and vegetables, whole grains, nuts, fish and legumes. This combination of foods makes up in large part what is commonly known as the Mediterranean diet, which has been associated with better cognitive functioning and lower risk for AD. However, the findings are mixed and the underlying mechanisms of involved micronutrients remain unclear (Allès et al., 2012; Engelhart et al., 2002; Roberts et al., 2012a; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006; Vassallo & Scerri, 2013). For example, vitamin C has been hypothesized to improve memory (Perrig, Perrig, & Stahelin, 1997), vitamin E has been reported to delay time to institutionalization in patients with AD (Sano et al., 1997), and the combination of the two has been suggested to improve cognitive function in late life and decrease the incidence of vascular dementia (Masaki et al., 2000) and AD (M. C. Morris et al., 1998; Zandi et al., 2004). In addition, high intake of flavanoids has been associated with reduced risk for AD, while other micronutrients such as a-carotene, b-carotene, lycopene, b-cryptoxanthene, a-tocopherol, folate, and cobalamine have been significantly correlated with memory performance (Commenges et al., 2000; Haller,

Weggemans, Ferry, & Guigoz, 1996). In the Cache County Memory Study, Wengreen and colleagues (2007) also found a positive relationship between intake of vitamin C, vitamin E, and carotene and cognitive function among older adults, especially when the source of these antioxidants was food rather than supplements.

Other research indicates that the overall quality and complexity of diet, rather than the specific importance of a given micronutrient, is critical in healthy aging. Wengreen, Neilson, Munger, and Corcoran (2009) found that those who consumed a more diverse diet from foods recommended by the U.S. Department of Agriculture (USDA) and Department of Health and Human Services (HHS) experienced significantly less cognitive decline over 11 years compared to those whose diets were less varied. This study controlled for several factors including education, age, gender, Apolipoprotein E (APOE) genotype, physical activity, use of nutritional supplements, total caloric intake, medical comorbidities and a variety of other health-related habits.

Also supportive of a complex conceptualization of the relationship between diet and cognitive health, Roberts and colleagues (2012b) indicated the importance of a healthy ratio of macronutrients in diet after examining the relationship between proportions of energy provided by macronutrients and risk for mild cognitive impairment (MCI) or dementia. Researchers in this population-based study in Rochester, Minnesota, followed 937 older adults (median age = 79.5) for approximately 3.7 years and stratified the percentage of daily energy intake by macronutrients, showing that risk for developing MCI or dementia was elevated in subjects with a high percentage of energy from carbohydrate intake at baseline. Conversely, subjects with high percentages of energy

from fat and protein intake at baseline were at reduced risk for developing MCI or dementia at follow-up. The model controlled for health problems such as type 2 diabetes, coronary heart disease, hypertension, stroke and depressive symptoms, as well as frequency of physical exercise, BMI, and presence of the APOE ε4 allele.

In addition to dietary factors of macro- and micronutrients, weight and BMI appear to play a key role in cognitive health. Progression to severe disability in dementia is commonly accompanied by significant weight loss (Albanese et al., 2013; Barrett-Connor, Edelstein, Corey-Bloom, & Wiederholt, 1996; Guerin et al., 2005; White, Pieper, Schmader, & Fillenbaum, 1996). In fact, the nationwide Consortium to Establish a Registry for Alzheimer's Disease (CERAD) study found that nearly twice as many patients with AD (mean age [*SD*] = 71.3 [7.75]) experienced clinically significant weight loss (≥ 5% change) compared to similar aged controls (mean age [*SD*] = 69.5 [*7.5*]) over 1 year (White et al., 1996). Researchers from the prospective Etude Longitudinale de Suivi de la Maladie d'Alzheimer (ELSA) study in Toulouse, France, compared risk factors for two different modes of weight loss based on a cohort of 395 patients (mean age [*SD*] = 75.5 [6.7]) with AD. Progressive weight loss (weight loss > 4% in 1 year), rather than severe weight loss (weight loss > 5 kg in 6 mos.), was associated with dementia severity, as measured by the Reisberg scale, and cognitive decline, as measured by the Mini Mental State Exam (MMSE), a common screening tool for detecting the existence and severity of cognitive impairment (Guerin et al., 2005).

The National Institute on Aging conducted an international epidemiological study to investigate the relationship between weight loss and severe dementia (Albanese et al.,

2013). Researchers surveyed 16,538 individuals aged 65 and older between January 2003 and July 2010 in several low and middle-income countries (LAMIC) including Mexico, Peru, India, China, Cuba, the Dominican Republic, Venezuela, and Puerto Rico. Clinically significant weight loss was categorized as weight loss of 10 or more pounds during the past 3 months. Severity of dementia was measured using the Clinical Dementia Rating scale (CDR). CDR scores were independently associated with weight loss in subjects of all countries with the lowest amount of weight loss occurring in participants with a CDR score of 0 (no dementia) and the highest amount of weight loss occurring in participants with a CDR score of 2/3 (moderate to severe dementia). Those who experienced greater weight loss were more likely to be older, female, and with fewer years of education, and fewer household assets (e.g., motor vehicle, TV, electricity, etc.). Interestingly, there was no correlation between weight loss and arm or waist circumference.

While changes in food preference and functional impairment may affect weight loss over the course of dementia, the association appears more complicated. Fluctuations in weight observed in people with dementia can appear before cognitive and functional manifestations of the disease, and may be related to age of onset and gender. For example, one population-based, prospective study of older adults in Rancho Bernardo, California showed that weight loss preceded the onset of AD. Compared to controls, both men and women who went on to develop AD in late life (early to mid-80s) experienced more weight loss approximately 7 years before onset of the disease (Barrett-Connor et al., 1996).

Research shows that an individual's weight as early as age 40 may be indicative of future risk for developing dementia; however at this stage of life, obesity and elevated BMI, rather than weight loss, appear to be risk factors for developing dementia later in life. In a population-based prospective study of an ethnically diverse cohort in California (68.6% White, 21.7% Black, 5.1% Asian, 4.6% other), obesity (BMI ≥ 30) at mid-life (age 40-45) was associated with a 75% increased risk of developing dementia 25-30 years later compared to normal weight (BMI = 18.6-24.9) at midlife. Those who were overweight (BMI = 25-29.9) were at a 35% greater risk of developing dementia compared to normal weight individuals. Interestingly, when statistical models were stratified by sex, the association between BMI and late-life dementia was significant for women but not for men. In addition, no racial differences were found between BMI and risk for dementia (Whitmer et al., 2005).

Two population-based studies in northern Europe found comparable results regarding midlife weight factors (Kivipelto et al., 2005; Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005). Researchers from the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study of 1,449 Finnish women and men found that only obesity (BMI > 30) at midlife (mean age [*SD*] = 50.6 [6]) was predictive of dementia and AD at follow-up (mean age [*SD*] = 71.6 [4.1]). Similarly, Rosengren and colleagues found a linear association between higher than normal BMI (BMI > 22.49) at mid-life (mean age [*SD*] = 52.6 [2.1]) and risk for developing dementia later in life (mean age [*SD*] = 77.2 [3.9]) in their Primary Prevention Study of 7,404 males from Goteborg, Sweden. Rosengren and colleagues demonstrated that these effects remained after controlling for other

cardiovascular and health risks. These findings contrast with those previously discussed from Whitmerand colleagues, which showed nonsignificant effects for men. Although unrelated to midlife weight factors, results from the population-based, longitudinal Cache County Study further demonstrate gender differences in weight patterns among individuals that later developed AD and vascular dementia (VaD). Specifically, obesity at baseline was significantly associated with subsequent dementia at a follow-up of approximately 3.2 years in females but not males aged 65 and older when controlling for age, education, APOE ε4 allele, and medical comorbidities (high cholesterol, diabetes, stroke, coronary artery bypass graft surgery (CABG), and myocardial infarction (MI) (Hayden et al., 2006).

Malnutrition in Elderly and Dementia Populations

Malnutrition, characterized by insufficient caloric intake, weight loss, deterioration of muscle mass, and poor appetite is a frequent problem in the elderly and has been associated with cognitive and functional impairment. Overall nutritional status in the elderly is commonly assessed by the Mini Nutritional Assessment (MNA), a well-validated screening tool for malnutrition (Guigoz, Vellas, & Garry, 1994; Vellas et al., 1998). The MNA uses a variety of health factors to quantify nutritional status including anthropometric (e.g., BMI, mid-arm circumference), general health (mobility, number of prescriptions, psychological well-being), dietary (type, amount and frequency of food intake), and subjective indicators (self-view of nutritional status). These health factors are quantified into a numerical score, which signifies “malnourishment,” “at risk for

malnutrition," or "well-nourishment" by the following cut-offs: less than 17, 17-23.5, and 24-30, respectively. In addition to identifying nutritional status in both elderly and dementia populations, the MNA has been used to establish links between overall nutritional status and functional, cognitive, and neuropsychiatric impairments in AD (Guerin et al., 2005; Saragat et al., 2012; Soto et al., 2008; Spaccavento et al., 2009; Vellas et al., 2005).

In their Italian clinic-based study, Spaccavento and colleagues (2009) evaluated 49 outpatients who were admitted to their Alzheimer's Disease Unit between 2001-2003 and diagnosed with AD according National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Cognitive, nutritional, functional, and psychiatric domains were assessed using the MMSE, Mental Deterioration Battery, MNA, Activities of Daily Living (ADL), Instrumental Activities of Living (IADL), and the Neuropsychiatric Inventory (NPI). ADLs primarily consist of basic self-care tasks such as dressing and feeding while IADLs are characterized as tasks that are not necessary for fundamental functioning but enable a person to live independently (e.g., care for others, home maintenance, financial management). The NPI assesses the occurrence, frequency, and severity of 10 common behavioral symptoms of dementia (e.g., apathy, irritability, delusions and others). The subjects were divided into two groups based on MNA scores. Of the 49 patients, 21 scored less than 23.5 on the MNA and were, therefore, considered at risk for malnutrition. The remaining 28 scored above 23.5 and comprised the well-nourished group. Researchers did not find significant differences between the two groups

on the MMSE and all of the Mental Deterioration Battery except for the ideomotor praxis test. However, there were significant differences between groups in both functional and neuropsychiatric domains. Patients who were at risk for malnutrition scored significantly lower on the ADL and IADL scales and experienced significantly more neuropsychiatric symptoms including hallucinations, agitation, depression, anxiety, apathy, aberrant motor behavior, and night-time disturbances ($p < 0.05$). Interestingly, the two groups did not differ in clinical features of weight or BMI, suggesting that these dimensions did not contribute to their MNA classification. In addition, the group at risk for malnutrition was significantly older than the well-nourished group.

In the prospective French REAL study, Vellas and colleagues (2005) demonstrated that patients at risk for malnourishment at baseline as assessed by the MNA progressed more rapidly over the course of a year compared to well-nourished patients, as evidenced by a dramatic decrease on the MMSE. This analysis was based on data from 523 Alzheimer's patients from the Alzheimer Centre of the Department of Internal Medicine and Clinical Gerontology at the Purpan University Hospital in Toulouse, France. At the study's initial evaluation in 1994, patients presented with AD according to the DSM-IV and NINCDS-ADRDA criteria and upon final inclusion, patients underwent biological (i.e., CT scan and thyroid test) and neuropsychological measures of AD. Follow-up included evaluation of cognitive status by MMSE, disability by ADL and IADL, and nutritional status by the MNA. In addition to a decrease in cognitive capacities, patients who were at risk for malnutrition at inclusion were more likely to become more dependent on caregivers after one year. In an ancillary report using the

same study cohort, Guerin and colleagues (2005) compared three different groups: well-nourished, at risk for malnourishment, and malnourished, and found that patients with AD who were the most malnourished exhibited dramatic impairments in cognitive, functional, and behavioral domains as measured by the MMSE, IADLs and the NPI. In addition, caregivers of malnourished patients experienced significantly more burden than those who cared for patients without nutritional problems. Finally, in agreement with Spaccavento and colleagues (2009), patients in this cohort who were at risk for malnutrition were significantly older than well-nourished patients.

Soto and colleagues (2008) presented descriptive data from an observational study conducted on 492 patients with AD and dementia who were hospitalized in 2005 in the Special Acute Care Unit (SACU) at the Toulouse University Hospital. Patients underwent a full clinical evaluation, gait and balance disturbance, and measures of cognitive, functional, nutritional, and neuropsychiatric status including MMSE, ADL, BMI, MNA, and NPI. The mean age (SD) of this cohort was 81.1 (7.7). With a mean (SD) MNA score of 17.9 (5), the majority of patients had poor nutritional status. Neuropsychiatric disturbances were the most prevalent symptoms during hospitalization, including anxiety, depression, agitation-aggressiveness, sleep disorders, wandering, apathy, delusions and hallucinations, with an average of two abnormalities on the NPI per patient. Cognitive and functional outcomes were also low as exhibited by mean (*SD*) scores of 14.5 (7.4) on the MMSE and 3.7 (1.7) on the ADL.

A recent cross-sectional study in Cagliari, Italy found significant impairments in nutritional status and functional capacities in elderly patients with mild to moderate AD

compared to those without AD; however, these researchers did not find a significant relationship between MNA score and functional outcomes in those with AD (Saragat et al., 2012). Participants included 83 independently living individuals (29 men and 54 women) aged 66-96 years old with mild-moderate AD and 91 age-matched controls (37 men and 54 women). While nutritional status was evaluated using the MNA, psychological and functional measures included the MMSE, ADL, IADL, and Geriatric Depression Scale (GDS). Interestingly, better nutritional status as determined by the MNA predicted better performance on the MMSE, GDS, ADL and IADL for those without AD but not for those with AD. Anthropometric variables were more strongly associated with cognitive and functional outcomes in AD patients. In particular, obesity as measured by BMI was highly correlated with worse scores on the MMSE, ADLs, and IADLs, and abdominal obesity as measured by waist circumference was significantly related to worse scores in IADLs. Furthermore, bioelectrical impedance vector analysis (BIVA), a measure of body composition that can be used for malnutrition screening, results predicted worse performance on the MMSE, GDS, and ADLs in female patients with AD compared to controls and worse scores on GDS in males with AD. These findings suggest that the severity of dementia symptoms may relate primarily to body composition variables, particularly fat to muscle ratio, and significant gender differences may be involved.

The level of malnutrition in dementia patients may be highly influenced by their degree of physical activity. Specifically, nutrition and exercise may act synergistically to produce positive health effects in AD patients. In fact, Rolland and colleagues (2000)

found significant improvements in MNA score in 23 patients with AD (mean age [range] = 78 [71-92]) following an endurance exercise intervention of walking and use of stationary bicycle implemented for an average of 7 weeks. Exercise has also been reported to independently reduce functional impairments in AD. In their population-based study, Kwak, Um, Son, and Kim (2008) found that an anaerobic exercise program involving 30- to 60-minute muscle conditioning and stretching routine using light weights and resistance bands 2-3 times per week for 12 months was associated with significant increases in scores on both MMSE and ADLs in patients with dementia compared to controls at the 6 and 12 months post intervention. Furthermore, in their experimental study of 134 AD patients in a nursing home, Rolland and colleagues (2007) later found that regular moderate exercise (1 hour sessions twice a week), consisting of walking, stretching, balancing and strengthening, led to clinically significant improvements in ADL compared to AD patients who received routine medical care (no specific exercise or behavioral management training).

Summary of the Literature in Nutrition and Dementia

In summary, nutrition serves as an important variable in maintaining cognitive integrity throughout the lifespan. Key nutritional factors include diet, weight, and BMI. While a diet high in carbohydrates is a risk factor for developing MCI or dementia, a diet high in protein and fats is related with a decreased risk. It may not be surprising then that adherence to the Mediterranean Diet, which is high in antioxidants, polyunsaturated fats, and DHA Omega-3 fatty acids, is also believed to benefit cognitive health. Weight and

BMI have been researched extensively in relation to cognitive and functional impairment in dementia. Risk for dementia is both associated with obesity at mid and late life and acute, clinically significant weight loss. In addition, age and gender may interact with weight to predict risk for dementia. These components are among those used to establish malnutrition, as estimated by the MNA, in elderly populations. Although the MNA does not account for discrete energy intake from carbohydrates, fats, and protein, it does include information of the broad food groups from which these macronutrients are derived.

In studying the role of nutrition in dementia populations, researchers have used the MNA as an indication of overall nutritional status and related it to cognitive, functional, and neuropsychiatric outcomes in dementia. Low MNA scores indicative of malnutrition or risk for malnutrition have been correlated with low scores on the MMSE, ADL, and IADL, and elevated scales on the NPI. However, the predictive value of nutritional status on the progression of neuropsychological domains in people with dementia has not yet been explored. Furthermore, critical elements of malnutrition or associated factors (diet, weight, BMI) for predicting progression of neuropsychological impairment have not been established. A more detailed understanding of these relationships may lead to intervention strategies aimed at maintaining higher levels of neuropsychological functioning and level of functioning. For example, preservation of executive functions may be more beneficial for maintaining greater independence than memory alone. The current study aims to explore some of the primary factors related to malnutrition (BMI and diet) as well as overall nutritional status as assessed by the MNA

in relation to neuropsychological functioning in AD and other dementias.

Research Questions

In order to investigate the role of nutritional status on the neuropsychological symptoms of dementia, the association of the mMNA and other nutritional factors with outcomes on neuropsychological measures was examined in a sample of individuals with AD and other dementias. The research questions were:

1. Does nutritional status and intake change over the course of dementia?
    a. How does mMNA score change over time in persons with dementia and what factors (e.g., dementia type, duration and demographics) predict mMNA?
    b. How does intake of carbohydrates, protein, fruits and vegetables change over time and what factors (e.g., dementia type, duration and demographics) predict these changes?

Based on the literature, it was expected that the nutritional status would decline, complexity of diet would decrease, carbohydrate intake would increase, and overall caloric intake would decrease as dementia progressed, with individuals consuming smaller, less frequent meals comprised of fewer food groups.

2. What is the association between nutritional status as determined by the mMNA and progression of neuropsychological impairment in memory, expressive language, executive functioning, and visuospatial skills in persons with dementia? Based on evidence implicating the role of nutrition in the risk for and progression of AD, it was

hypothesized that higher mMNA scores, indicative of better nutritional health, would be associated with better neuropsychological test scores and slower decline on test scores over time.

3. Are specific mMNA components (BMI and intake of protein, carbohydrates and fruits and vegetables) associated with neuropsychological outcomes of memory, expressive language, executive functioning, and visuospatial skills in dementia progression? Based on the literature it was hypothesized that a BMI indicative of severe weight loss would predict poorer outcomes on neuropsychological outcomes. It was also hypothesized that individuals with higher consumption of meat, poultry, fish, legumes, and dairy in comparison to grains would show better neuropsychological test scores and slower rates of decline. Furthermore, it was hypothesized that individuals with high intake of antioxidants would experience slower rates of decline on neuropsychological tests versus individuals with low intake of anti-oxidants.

4. What additional factors, if any, affect the associations between total mMNA score and neuropsychological outcomes as examined in Question 2, and what factors affect the associations between signs of malnutrition and neuropsychological outcomes as examined in Question 3? Relevant factors identified from the literature review included type of dementia, gender, overall health, neuropsychiatric symptoms, age of dementia onset, dementia severity, education and level of physical activity.

CHAPTER III

METHODS

This study used extant data from the Cache County Dementia Progression Study (DPS), which followed participants identified with incident dementia through the Cache County Study on Memory in Aging (CCSMA). Breitner and colleagues (1999) described the dementia screening and data collection process of CCSMA in detail. The following sections will outline the sample characteristics, data collection methods, and assessment protocol relevant to the current investigation, as well as the proposed statistical analysis to interpret this data.

Cache County Study on Memory in Aging Recruitment Procedures

CCSMA began in 1995 by approaching all Cache County residents age 65 and older for research participation. Throughout the enrollment process, 98 had moved out of the area, 207 had passed away, and 559 had refused or were not found. Of the 5,956 residents who were originally contacted, 5,092 completed enrollment. Upon enrollment, all participants were characterized based on a variety of demographic variables and risk factors including education, age, APOE genotype, overall physical and psychological health (depression), and medical and family history. The Institutional Review Boards at Utah State University, Duke University, and the Johns Hopkins University approved all procedures conducted by CCSMA.

Dementia Ascertainment

Cases of dementia were ascertained in four, triennial waves, implementing a multi-staged screening and assessment protocol. At baseline, CCSMA staff used the Modified Mini Mental State Exam (3MS) to screen participants for cognitive impairment. Those who scored below the 25th percentile (sensory-motor and education adjusted 3MS score < 87) were followed up with the Dementia Questionnaire (DQ) with a knowledgeable informant. The DQ queried symptoms and medical exclusions of dementia and were rated by a study neuropsychologist or geropsychiatrist as: (1) no impairment, (2) mild dysmnesia or other mild difficulty, (3) moderate cognitive difficulty probably not meeting criteria for dementia, (4) questionable dementia, and (5) probable dementia. Individuals who scored a 4 or 5 on the DQ were evaluated for dementia in a clinical assessment (CA), which included a review of medical history, blood pressure testing, neurological exam, assessment of behavioral symptoms by the NPI, determination of overall dementia severity by the Dementia Severity Rating Scale, and administration of a one hour neuropsychological battery. All testing was conducted by a nurse or psychometrist at the participants' place of residence in the presence of an informant. Slight deviations from this procedure were made with modified screening cut-points in Waves 2-4 to increase the sensitivity of the procedures to identify milder forms of cognitive impairment; the DQ phase was eliminated in Waves 3 and 4.

Diagnosis of Dementia

To determine dementia status, the CA team and a study geropsychiatrist and

neurologist assigned preliminary diagnoses of dementia following DSM-3R criteria (APA, 1987). Those classified with dementia or its prodrome were further evaluated with neuroimaging and laboratory tests to rule out systemic causes of cognitive impairment. Differential dementia diagnoses were made using all available data in diagnostic conferences where all available clinical data were reviewed by a panel of clinicians with expertise in geropsychiatry, neurology, and neuropsychology. AD and VaD were diagnosed using 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) and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN; Román et al., 1993) criteria, respectively. Four hundred seventy incident dementia cases were identified over three waves of data collection in CCSMA. Of these participants, 328 (69.8%) were considered to have probable or possible AD and the remaining 142 (30.2%) were diagnosed with other forms of dementia.

Dementia Progression Study

In 2002, researchers contacted the surviving participants of CCSMA who were diagnosed with dementia and conducted a longitudinal follow-up study known as the Cache County Dementia Progression Study (DPS; Tschanz et al., 2011). Participants and their informants were visited semiannually for follow-up interviews and testing. Interviews with the informants were conducted to gather the following information about

the participant: updated medical history (i.e., medical conditions and medications), nutrition, neuropsychiatric symptoms, and involvement in mental and physical activities. Testing with the participants included a brief neurological and physical exam and measures of both general cognition and specific neuropsychological domains. The total number of participants enrolled in the DPS was 328.

Selection Criteria

The analyses conducted for the current study examined participant data collected during the odd DPS visits. Because of the attrition in later visits, participant data were included for up to 6 years of visits. Participants were selected if they were not missing data for any of the predictor variables, dependent variables, or covariates. Data from neuropsychological evaluations was also included if testing was completed according to standard protocol.

Independent Variables

Nutritional Status

Nutritional status was determined using a modified MNA (mMNA), derived from the original MNA. As noted previously, the MNA is an 18-item screening tool for malnutrition in the elderly, conveniently succinct for use in primary medical settings (Guigoz et al., 1994). The MNA was developed and validated against physician evaluation and biological markers (weight loss and albumin levels) of malnutrition across three different populations of frail and healthy elderly participants between 1991 and

1993 in Toulouse, France, and Albuquerque, New Mexico. It was determined to have a sensitivity of 96%, specificity of 98%, and predictive value of 97% for assessment of malnutrition risk before severe changes in weight and albumin levels occur (Vellas et al., 1998). MNA score is based on four rubrics: anthropometric assessment, medical assessment, short dietary assessment, and subjective assessment. The current study matched items from the nutrition interview conducted by a nurse in the DPS follow-up study to items on the MNA in order to generate the mMNA. Some questions in the general and subjective rubrics of the MNA that investigate the presence of dementia or depression and the patient's self-view of nutritional status were either unreliable in self-report or possible confounding variables for the present study and were therefore excluded. In addition, information for two other MNA items, one regarding the presence of pressure sores of skin ulcers and another concerning calf-circumference, were not collected during the original nurse interview and therefore omitted from the mMNA. Consequently, the mMNA consists of 14 rather than 18 items and includes three rubrics: anthropometric, medical, and dietary. Using similar cutpoints as the original MNA, but adjusted to the new total scores, yielded the following new cut-offs for the mMNA (22 points maximum): <12.5 = malnourished, 13-17.5 = risk for malnutrition, ≥ 17.5 = well-nourished. See Appendix A for the mMNA items and the DPS dataset from which each was derived.

Body Mass Index

Weight and height were recorded every 6 months. This study used annual observations. BMI was calculated using the following formula:

$$\frac{\text{Mass (kg)}}{\text{Height (m)}^2}$$

Dietary Components

A nutritional assessment was conducted annually during DPS follow-up. From this data, information about the frequency of fruit and vegetable consumption as well as dietary intake from sources of animal protein, plant protein, dairy protein, and carbohydrates, was ascertained. Each question on the nutrition assessment that was used in the present study had the following available responses: six or more times a day, four or five times a day, two or three times a day, one time a day, five to six times a week, two to four times a week, one time a week, one to three times a month, none or less than one time a month, or don't know. Each food group was analyzed as a continuous variable after values were transformed into daily estimations of frequency. See Appendix B for complete nutritional assessment. Note that the numbers following each response were for data entry purposes and do not indicate numerical value of response.

Fruits and vegetables. Fruit and vegetable consumption was measured by the following question: "How often does (NAME) usually eat fruits or vegetables (canned, fresh, frozen, or juice)?" See item J4 in Appendix B.

Carbohydrates. This questionnaire measured several forms of grain products, such as sweets, bread, cereal, pasta and rice. For questions regarding intake of grains, see items J5-J7 of Appendix B.

Protein. The consumption of protein-rich foods such as fish, poultry, pork, beef, soy, beans, legumes, and dairy products are found in items J8-J9 of Appendix B.

Patterns of protein and carbohydrate consumption. The relative consumption of protein and carbohydrates was analyzed in two ways. Based on the distribution of protein and carbohydrate intake at baseline, a time-varying categorical variable of protein and carbohydrate consumption patterns was created to demonstrate the following patterns: 5 - low protein-high carbohydrate, 4 - low protein-low carbohydrate, 3 - high protein-low carbohydrate, 2 - high protein-high carbohydrate, and 1 - all others. Since the high and low cut-offs were assigned based on the tertiles of protein and carbohydrate consumption at baseline, the "all others" category includes combinations including the middle tertiles. The low protein-high carbohydrate category was used as the reference category based on past literature demonstrating a higher risk for developing dementia for those who have this pattern of energy intake. The second method tested the interaction of continuous protein and carbohydrate consumption variables (protein*carbohydrate), which may capture moderation effects otherwise lost in the category method.

Additional Covariates

During data analysis, several factors were be tested as potential covariates to the relationship between neuropsychological assessments and nutritional variables, including type of dementia, age, gender, education, neuropsychiatric symptoms, and level of physical activity. Dementia severity and caregiver coresidence were also tested in the modeling of mMNA trajectory, while place of residence and overall health (all time-varying) was tested in modeling of food trajectories.

Type of dementia. During the diagnostic phase of the Cache County Study on Memory in Aging, individuals with AD and VaD were classified as such by NINCDS-

ADRDA and NINDS-AIREN. Approximately 30% of those identified with dementia were diagnosed with some other type of dementia. Dementia type was categorized as AD, VaD, and the heterogeneous category of "other dementia." Other dementias included Frontal Lobe dementia, Lewy-Body dementia, Pick's disease, Parkinson's disease, and dementias of unknown etiology.

Demographic variables. Age, gender, and education were collected upon enrollment of CCSMA, while place of residence and caregiver coresidence were collected at semiannual DPS visits.

Neuropsychiatric Symptoms. The Neuropsychiatric Inventory (NPI; Cummings et al., 1994), an assessment of ten behavioral disturbances, was administered during all waves of DPS data collection. The NPI is a validated measure of both neuropsychiatric symptom frequency and severity in persons with dementia. Overall internal consistency reliability has been demonstrated with a Chronbach's alpha of 0.88. Interrater reliability varies by behavioral category with 93-100% and 89.4-100% between rater agreement of frequency and severity, respectively. Overall test-retest reliability has been reported as $r = 0.79$ for frequency and $r = 0.86$ for severity, although this also varies by behavioral category with frequency correlations ranging from $r = 0.51$-0.98 and severity correlations ranging $r = 0.51$-0.87 (Cummings et al., 1994).

Level of physical activity. Nurse evaluations conducted during DPS visits included a physical activities questionnaire, which measured the subject's frequency, amount and type of exercise over the previous 12 months. Each physical activity was quantified by frequency of each occurrence and average amount of time spent doing that

activity upon each occurrence. For the present study, frequency and duration of each endorsed activity were summed across activities to create an overall total of hours of physical exercise per month. See Appendix C for the full physical activities questionnaire.

Overall health. The General Medical Health Rating (GMHR; Lyketsos et al, 1999) is a short rating scale of global health and medical comorbidity that was completed during the nursing assessment at each DPS visit. This measure was designed specifically for use in patients with dementia. Interrater reliability for the GMHR is high with a weighted kappa of 0.93. In addition, the GMHR has high concurrent and predictive validity for overall health status (Lyketsos et al., 1999).

Dementia severity. The Clinical Dementia Rating Scale Sum of Boxes (CDR-sb; Hughes, Berg, Danzinger, Coben, & Martin, 1982) sums ratings across six domains (memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care) to determine the severity of cognitive and functional impairments. This rating method has demonstrated 94% accuracy in diagnosing dementia stages (O'Bryant et al., 2010). The CDR was completed at each DPS visit.

Dependent Variables

Cognitive status was evaluated based on a battery of neuropsychological measures administered at the same visit as the mMNA was completed. These consisted of the CERAD-Neuropsychological Battery (CERAD-NP; J. C. Morris et al., 1989; Welsh et al., 1994) and the 30-item Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983). CERAD-NP is a well-validated measure sensitive to the progression of AD with

excellent test-retest (r = 0.80-0.91) and interrater (r = 0.92-1.0) reliabilities (Fillenbaum et al., 2008). The CERAD-NP subtests used in the current study evaluate memory, expressive language and semantic memory, and visuospatial ability. One modification was made to the CERAD subtests. Rather than use the CERAD Naming Test, a 15-item version of the BNT, this study used a 30-item BNT to improve sensitivity to milder forms of cognitive impairment. The 30-item BNT has demonstrated good reliability and high correlation with the full BNT, which has good validity, test-retest reliability with most studies reporting $r > 0.9$, high internal consistency (r = 0.78-0.96; Strauss, Sherman, & Otfried, 2006). Only annual test scores corresponding to the administration of the nutritional questionnaire were used. A review of each test and neuropsychological domain used in the current study follows.

Memory

Measures of memory included the CERAD Word List Memory (WLM) and the recognition CERAD Constructional Praxis tests. The WLM consists of several 10-word lists used to assess immediate and delayed memory as well as recognition. In order to evaluate immediate memory with the WLM, the test administrator asks the test-taker to read aloud a list of ten words and then recall as many words as possible. This process is repeated two more times using two additional lists for a total of three trials. Each trial is scored by the number of correct recalled words for a maximum of 30 points overall. Delayed memory is measured by asking the test-taker to recall the first list from the immediate memory trials after a 5-minute delay for a maximum score of 10-points (one point per correctly recalled word). Lastly, the test administrator asks the test-taker to

distinguish previously used words from new words using a list of 20 words comprised of the original list and 10 other "distractors." A point is given for each correct distinction for a maximum total of 20 points. Because persons with dementia generally score at the "floor" of the delayed word recall test, only immediate recall and recognition scores were analyzed in this project.

Constructional Praxis consists of a delayed memory assessment that requires the test-taker to draw four line drawings from memory after having copied them 10 minutes earlier, followed by a recognition test. The recognition test ranges from 0 - 4 points for correct identification of the drawing from three foils. The delayed memory score was not used in this analysis since most persons with dementia score at the floor of this measure.

Expressive Language

The CERAD verbal fluency and modified BNT were used to assess this domain. The BNT is a 60-item task in which test takers must name 60 images ranging from low to high difficulty based on the frequency that the corresponding words occur in the English language. This study modified the BNT by selecting and using only odd items from the BNT. Test administrators implement a cut-off time of 20 seconds per image. The total score is based on amount of correct answers for a maximum of 30 points. During the CERAD Verbal Fluency test, the test taker must mentally retrieve and verbally express the names of as many animals as possible within 1 minute. Each name counts as one point, excluding duplicates or variations of a previously used word (e.g., plural forms).

Visuospatial Skills

In addition to memory, the CERAD constructional praxis subtest measures visuospatial capacities. Each line drawing increases in difficulty (circle, diamond, overlapping rectangles, and cube) and is scored based on accuracy for a subtest total of 11 points.

Executive Functioning

CERAD verbal fluency is also a measure of executive function due to its switching and working memory components (Lezak, Howieson, Bigler, & Tranel, 2012). This test of semantic fluency poses the challenge of switching between subcategories within the larger category of animals. Test takers also had to hold previously named animals in working memory in order to effectively generate new animal names.

Statistical Analysis

General exploratory analysis was conducted to determine sample characteristics, attrition rates, survival patterns, and distributions across outcome variables over time. Linear mixed models were used to examine the relationship between the independent variable and each dependent variable as well as identify and control for covariates. Use of multi-level modeling techniques enabled accurate representation of the observed characteristics within participants across time as well as the variance of these characteristics between participants over time. The method assumes that the independent and dependent variables interact at both intra- and inter-individual levels over time controlling for all significant covariates. In addressing research question 1, linear mixed

models were used to examine the trajectories of nutritional status and food intake over time. Research question 2 examined the independent effect of overall mMNA score (continuous variable) on the scores of each neuropsychological test (continuous variables) with linear mixed models. In addressing research question 3, linear mixed models were used to investigate the association between each component of nutritional status and each neuropsychological test score. In addressing research question 4, covariates were added sequentially, comparing nested models by comparing negative 2-log likelihood values (-2LL) using the chi-square test of independence. Based on the literature review, important factors tested as covariates included type of dementia, age, gender, education, neuropsychiatric symptoms, overall health, dementia severity, level of physical activity, place of residence, and caregiver co-residence.

CHAPTER IV

RESULTS

Sample Characteristics

Of the 328 enrolled participants, 293 completed the mMNA at some point in time. These participants were comprised of 171 cases of AD, 31 cases of VaD without AD, and 38 cases of some other form of dementia. At this point, approximately half of the participants were experiencing mild dementia with a global CDR rating of 1.

Approximately half (165 or 56.3%) of the sample was comprised of females and the majority (289 or 98.6%) was White. At baseline, participants ranged in age from 73.22 to 105.95 with the mean (sd) of 85.62 (5.65). Mean age (*SD*) of dementia onset was 82.16 (5.95) years, ranging from 68 to 104, and mean (SD) dementia duration at baseline was 3.46 (1.89) years. The mean (*SD*) level of education was 13.32 (2.98) years with approximately 17% of the sample having completed less than a high school education. The majority of the sample (70.6%) was living at home upon enrollment. The sample had a mean (*SD*) NPI score of 8.80 (9.35) at visit one. Across participants, mean (*SD*) physical activity was 10.60 (18.68), with a range of 0-138.39 hours per month. Two extreme outliers (260.75 and 486.72 hrs/mo) were removed from the data set due to implausibility of values (these values suggest that the person with dementia was physically active for 8-16 hours per day).

Table 1 shows the differences between those with complete mMNA ($N = 293$) and those missing mMNA at baseline. Participants with missing mMNA scores tended to

Table 1

Baseline Participant Characteristics: mMNA Completers Versus Noncompleters

	mMNA (N = 293)				No mMNA (N = 35)					
Characteristics	*n*	%	Mean	*SD*	*n*	%	Mean	*SD*	Chi^2 value	*t*
Female	165	56.3			25	71.4				
Dementia type										
AD	211	7.0			25	71.4				
VaD	36	12.3			3	8.6				
Other dementia	46	15.7			7	20.0				
Residence*									16.406	
Home/outpatient	207	70.6			13	37.1				
Residential/assisted living	56	19.1			10	28.6				
Skilled nursing facility	29	9.9			10	28.6				
Missing	1	0.03			2	5.7				
Coresidency*									7.908	
Lives with CG	144	49.1			8	22.9				
Doesn't live with CG	124	42.3			22	62.9				
Missing	25	8.5			5	14.3				
CDR*									11.345	
0 - no dementia	2	.8			0	0.0				
0.5 - uncertain	67	23.3			1	2.9				
1 - mild dementia	147	51.7			19	54.3				
2 - moderate dementia	49	17.1			8	22.9				
3 - severe dementia	18	5.4			2	5.7				
4 - profound dementia	7	1.7			3	8.6				
5 - terminal dementia	0	0.0			0	0.0				
Missing	3	1.0			2	5.7				
Age*			85.62	5.65			88.73	5.75		3.068
Education			13.32	2.98			13.44	2.58		
Onset age*			82.16	5.95			84.29	6.12		1.993
Dementia duration*			3.46	1.89			4.44	1.83		2.917
NPI			8.80	9.35			10.20	8.45		
Physical activity			10.60	18.68			5.50	12.95		
BMI*			25.54	4.29			23.60	4.57		-2.300

*Significant differences between those with and without mMNA completion observed in independent samples *t* tests or chi^2 for independence ($p < .05$).

be older, female, and living in an institutional setting without an unpaid caregiver.

Presentation of the remaining results of this project is organized according each research question, with the exception of Research Question #4, an examination of covariates. Significant covariates for each model are discussed in the corresponding sections of each nutrition-related research question.

Research Question #1: Nutritional Fluctuations Over Time

mMNA and Rate of Change Over Time

mMNA trajectory. Mean (*SD*) mMNA score at baseline was 16.57 (2.94), indicating prominent risk for malnutrition (see Figure 1 for mMNA distribution). Table 2 shows baseline participant characteristics stratified by nutritional status at enrollment. There was a tendency for those with worse nutritional status to be female, develop

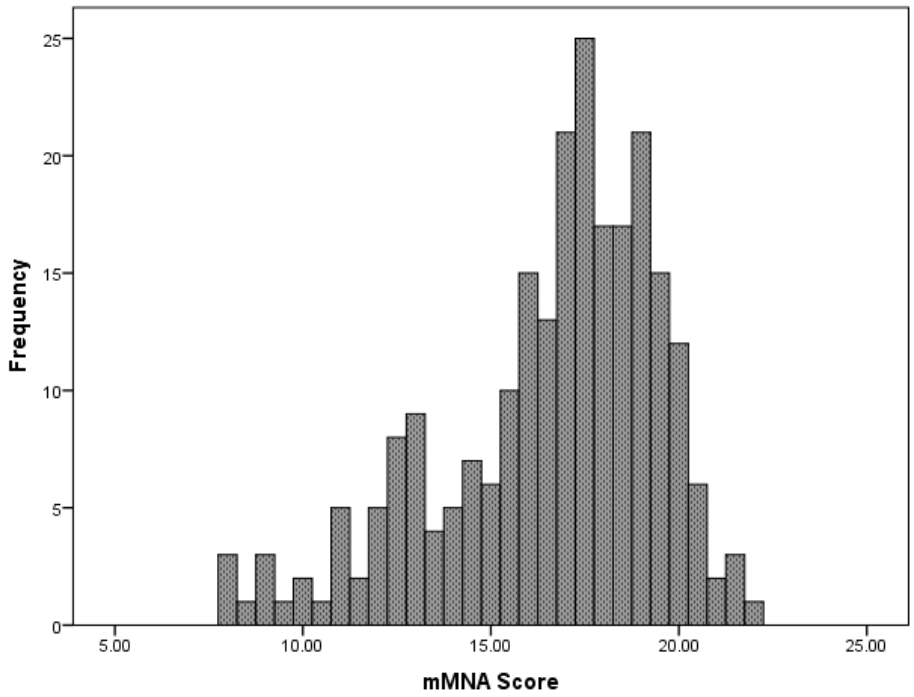

Figure 1. Baseline mMNA distribution.

Table 2

Baseline Sample Characteristics by Nutritional Status

	Malnourished				At risk for malnutrition				Well nourished					
Characteristics	*N*	%	Mean	*SD*	*N*	%	Mean	*SD*	*N*	%	Mean	*SD*	Chi^2 value	*F*
Nutritional status	31	12.92			115	47.92			94	39.17				
Female*	20	64.52			70	60.87			35	37.23			13.78	
Dementia type*													16.65	
AD	21	67.74			75	65.22			75	79.79				
VaD	0				19	16.52			12	12.77				
Other dementia	10	32.26			21	18.26			7	7.45				
Residence**													45.89	
Home/outpatient	11	35.48			77	66.96			87	92.55				
Residential/assisted living	12	38.71			27	23.48			7	7.45				
Skilled nursing facility	8	25.81			11	9.57			0					
Coresidency**													16.67	
Lives with CG	11	35.48			55	47.83			62	65.96				
Doesn't live with CG	19	61.29			54	46.96			22	23.40				
Missing	1	3.23			6	5.22			10	10.64				
CDR**													32.22	
0 - no dementia	0				0				2	2.1				
0.5 - uncertain	5	16.1			23	20			28	29.8				
1 - mild dementia	9	29.0			63	54.8			52	55.3				
2 - moderate dementia	11	35.5			18	15.7			12	12.8				
3 - severe dementia	4	12.9			9	7.8			0	0.0				
4 - profound dementia	2	6.5			2	1.7			0	0.0				
5 - terminal dementia	0	0.0			0	0.0			0	0.0				
Age*			87.83	6.54†			86	5.64			84.33	4.39		5.75
Education			13.23	3.29			13.14	3.1			13.50	2.87		
Onset age*			84.08	6.62†			82.45	6.12			81.09	4.67		3.64
Dementia duration			3.75	1.54			3.53	1.99			3.24	1.87		
NPI*			10.45	8.28			9.91	9.58†			6.59	8.60		4.18
Physical activity*			3.26	6.6†			9.36	18.33†			15.70	22.75		5.73
BMI**			21.93	3.42†‡			25.47	4.59†			27.05	3.56		19.31
Follow-up time			1.52	1.62			1.46	1.63			1.57	1.57		

Note. Fifty-three individuals were missing an mMNA score at visit one.

*Significant differences between mMNA groups observed in one-way ANOVAs or chi-square for independence $p < .05$.

** Significant differences between mMNA groups observed in one-way ANOVAs or chi-square for independence $p < .001$.

† significant difference compared to well based on Tukey HSD post-hoc analyses.

‡ significant difference compared to at risk based on Tukey HSD post-hoc analyses.

different patterns of dementia, and living in an institutional setting without an unpaid caregiver compared to those with better nutritional status. Those who were well-nourished were younger and had fewer neuropsychiatric symptoms than those who were malnourished and at risk for malnutrition, respectively. Furthermore, well-nourished individuals were more physically active and had higher BMIs than those in the other two groups, while malnourished individuals had significantly worse BMI than both groups.

A linear mixed effects model with time as the sole predictor indicated a significant decline in mMNA score over time ($p = .006$) by a factor of 0.22 points per year. With the inclusion of covariates, time became nonsignificant ($\beta = -.12$, $p = .108$; see Table 3). Variables significantly associated with mMNA scores included dementia onset age, gender, type of dementia, caregiver coresidence and CDR-sb. Each additional year older in onset age was associated with a 0.11 ($p < .001$) point decrease in the mMNA. Men had significantly better nutritional status overall, compared to women ($\beta = .78$, $p = .015$). Compared to those with "other" dementias, those with AD and VaD scored 2.08 ($p < .001$) and 1.43 ($p = .009$) points higher, respectively on the mMNA, suggesting that these participants were better nourished than those diagnosed with other dementias. Caregiver coresidence was tested in the model to indicate that those who lived with caregivers had better nutritional scores than those who did not coreside with caregivers ($\beta = 1$, $p = .001$). Each point increase on the CDR-sb was associated with a .21-point decrease on the mMNA, indicating that more severe dementia was associated with worse nutritional status ($p < .001$). The CDR-sb interacted with time was not significant and excluded from the final model ($p = .491$).

Table 3

mMNA Trajectory

Variable	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Intercept	23.97	2.21	283.42	10.85	< .001	19.62	28.32
Time (yrs)	-.12	.08	132.09	-1.62	.108	-.28	.03
Onset age	-.11	.03	273.04	-4.07	< .001	-.16	-.05
Males	.78	.32	268.02	2.45	.015	.15	1.40
Dementia type (compared to other)							
AD	2.08	.41	266.92	5.14	< .001	1.29	2.88
VaD	1.43	.54	239.64	2.64	.009	.36	2.50
CDR-sb	-.21	.03	473.01	-7.69	< .001	-.26	-.15
CG coreside	1.00	.30	429.69	3.34	.001	.41	1.58

Note. Dependent variable: mMNA score.

Dietary Fluctuations

To describe the various nutrient intake of the sample, baseline values are discussed. The number of participants with baseline carbohydrate, protein, and fruit/ vegetable consumption was 241, 230, and 243, respectively. Protein consumption was further dissected into animal and plant sources with 241 in the animal protein group and 232 in the plant protein group. Each unit in food consumption represented daily frequency of consumption. Mean (*SD*) carbohydrate intake at first visit was 4.72 (1.54) times per day while overall protein intake was 3.47 (1.34) times per day. At baseline, consumption of protein from animal sources was greater than that from plant sources with mean (*SD*) animal protein intake of 3.29 (1.28) times per day and plant protein intake of 0.18 (0.24) times per day. Fruit and vegetable intake at baseline was moderate, with mean (*SD*) of 2.63 (1.04) times per day. Figures 2-4 show histograms of three main food groups while Figures 5-6 show histograms of protein stratified by plant and animal.

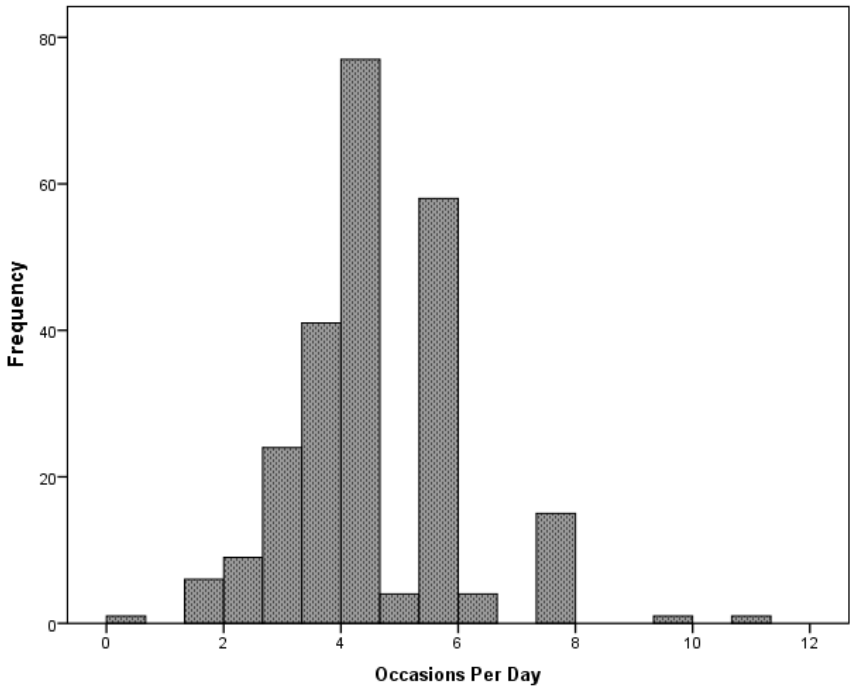

Figure 2. Frequency histogram of daily carbohydrate intake at baseline.

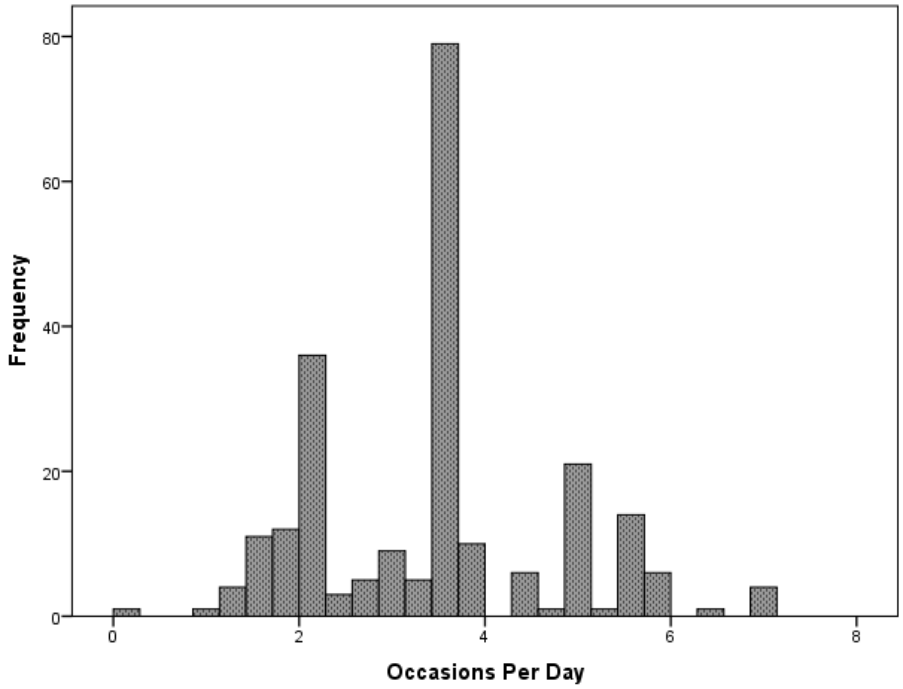

Figure 3. Frequency histogram of daily protein intake at baseline.

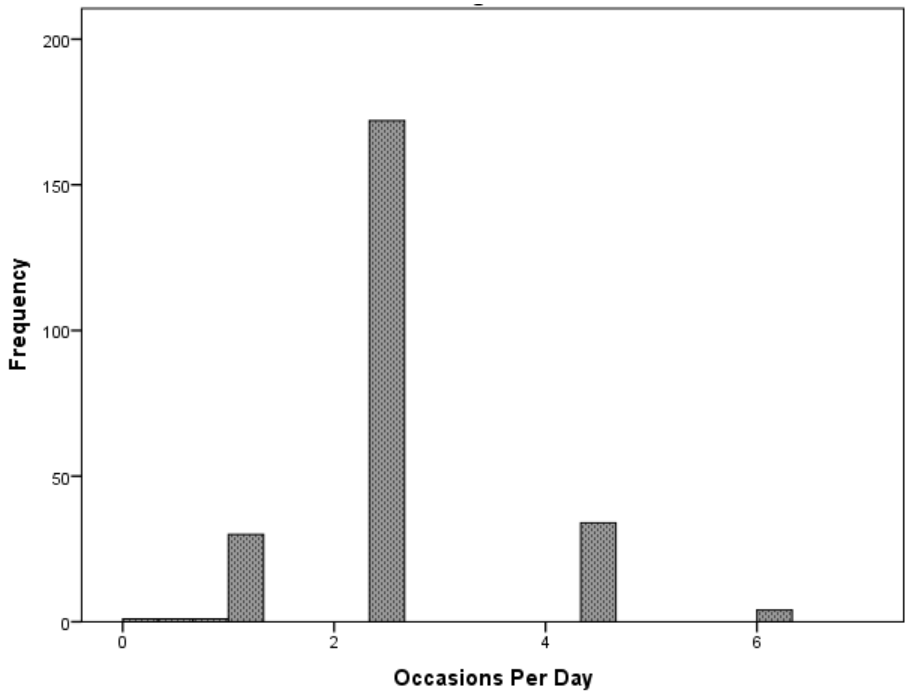

Figure 4. Frequency histogram of daily fruit/vegetable intake at baseline.

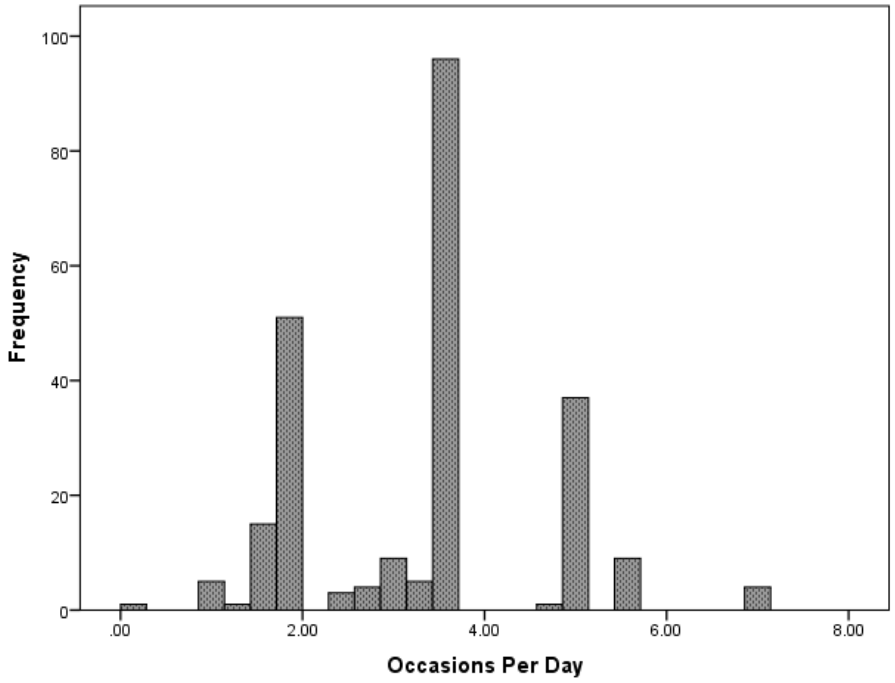

Figure 5. Frequency histogram of daily animal protein intake at baseline.

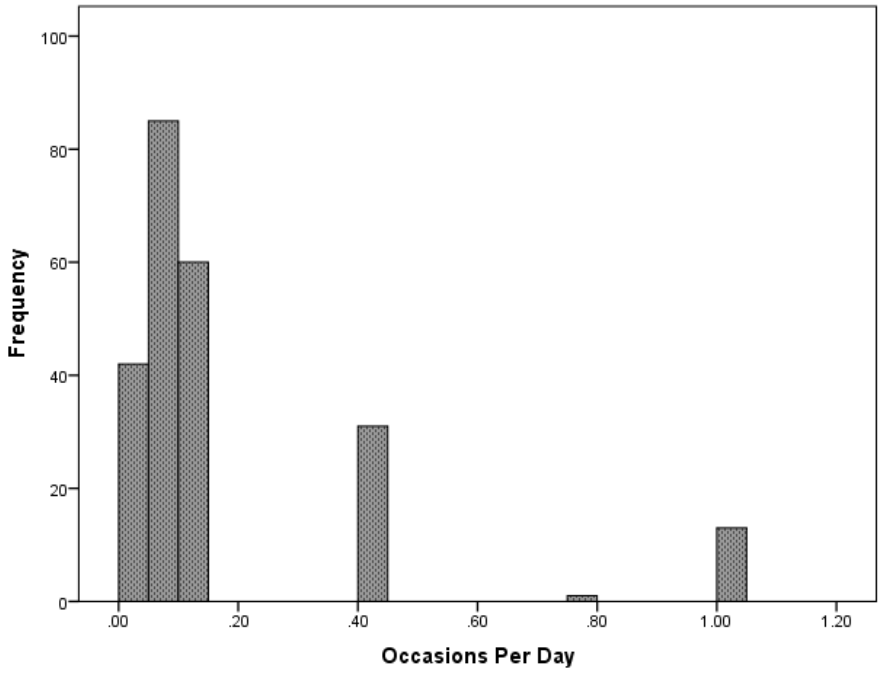

Figure 6. Frequency histogram of daily plant protein intake at baseline.

Carbohydrates. Carbohydrate intake decreased over time (β = -.09, p = .019). A nonlinear time^2 term was tested, but was not significant (p = .148). The time effect remained significant after controlling for dementia duration at baseline (see Table 4). For each additional year of having had dementia at baseline, the frequency of carbohydrates consumed increased slightly by .07 times per day over the course of the study (p = .025).

Protein. Protein intake over time trended downward but was not statistically significant (p = .152); however, this became significant with inclusion of covariates. Holding significant factors constant, each year in the study was associated with an overall decrease in daily protein consumption of .07 fewer occasions per day (p = .045; Table 5). Participant years of education (p = .026) and place of residence (p = .008) was associated with protein intake. Each additional year of education was associated with an increase

Table 4

Estimates of Fixed Effects for Trajectory of Carbohydrate Consumption

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Upper bound
Intercept	4.43	.14	315.81	32.09	< .001	4.16	4.70
Years	-.09	.04	141.21	-2.40	.018	-.16	-.02
Dementia duration	.07	.03	229.62	2.25	.025	.01	.14

Note. Dependent variable: Daily carbohydrate consumption (frequency).

Table 5

Estimates of Fixed Effects for Trajectory of Overall Protein Consumption

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Upper bound
Intercept	3.20	.33	316.67	9.75	< .001	2.56	3.20
Years	-.07	.03	142.23	-2.03	.045	-.14	-.07
Residence (compared to nursing home)							
Home	-.52	.20	442.17	-2.67	.008	-.90	-.52
Assisted living	-.21	.22	465.65	-.94	.349	-.64	-.21
Education	.05	.02	262.44	2.25	.026	.01	.05

Note. Dependent variable: Daily overall protein consumption (frequency).

of .05 occasions of protein consumption per day. Alternatively, living at home was associated with significantly less consumption of protein per day (.52 fewer occasions) compared to those in skilled nursing home facilities ($p = .008$). Caregiver coresidence was tested but nonsignificant ($p = .356$). Dementia severity was also tested in an attempt to explain the relationship between protein and place of residence, but was nonsignificant ($p = .260$) when place of residence was accounted for.

Modeling of animal and plant protein was then investigated separately. Linear mixed model of protein consumption derived from animal sources demonstrated statistically nonsignificant main effects for time (p = .121) and time^2 (p = .428). Analysis of change in plant protein intake failed to converge likely due to low frequency of intake.

Fruit and vegetables. Fruit and vegetable intake decreased linearly over time (β = -.08, p = .001); a non-linear time^2 term was not significant (p = .223). With the inclusion of covariates, decline in overall fruit and vegetable consumption remained significant, with a .08 (p < .001) reduction of daily intake per year (Table 6). Years of education (p = .001) and type of dementia (p = .032) were associated with frequency of fruit and vegetable consumption. Each additional year of education was associated with .05 higher fruit and vegetable intake per day. Compared to those with other dementias, individuals with AD and VaD had higher fruit and vegetable intake by .28 (p = .025) and .41 (p = .012) times per day, respectively.

Research Question #2: mMNA and Neuropsychological Functioning

mMNA and Word List Memory

As expected, WLM total scores declined over time (β = -.85; p < .001). Testing for a nonlinear trajectory by inclusion of time^2 term was not significant (p = .086). Higher mMNA score was associated with better average overall WLM scores (β = .29; p < .001), although mMNA was not significantly associated with *rate* of WLM change over time (interaction of mMNA x time; p = .611). This effect remained significant after inclusion of covariates. For each point increase in mMNA score, there was an associated .23-point

Table 6

Estimates of Fixed Effects for Trajectory of Fruit/Vegetable Consumption

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Intercept	1.70	.22	231.82	7.65	< .001	1.26	2.14
Years	-.08	.02	84.05	-3.93	< .001	-.13	-.04
Education	.05	.01	221.17	3.48	.001	.02	.08
Dementia type (compared to other)							
AD	.28	.13	301.59	2.25	.025	.04	.53
VaD	.41	.16	276.46	2.52	.012	.09	.73

Note. Dependent variable: Daily fruit and vegetable consumption (frequency).

increase in WLM. Significant covariates included dementia duration ($p < .001$) and subject NPI scores ($p < .001$) in that each additional year of dementia prior to baseline was associated with a .80 lower score in WLM and a one-point increase on the NPI was associated with a.08 point lower score in WLM. Table 7 displays the results of the linear mixed models.

mMNA and Word List Recognition Memory

WLR total scores declined over time ($\beta = -1.13$, $p < .001$; see Table 8). A nonlinear trajectory was tested with inclusion of time^2 but was nonsignificant ($p = .124$). Stepwise addition of mMNA and its interaction with time showed that mMNA was significantly associated with average WLR scores ($\beta = .48$, $p < .001$) as well as *rate* of WLR decline over time ($\beta = .12$, $p = .003$). With the inclusion of covariates, the association of mMNA and WLR remained. Specifically, every one-unit increase in mMNA was associated with a .13-point slower rate of decline per year on the WLR

Table 7

Linear Mixed Model of mMNA and WLM

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Intercept	9.30	1.25	558.35	7.47	< .001	6.86	11.75
Time (years)	-.63	.11	113.73	-5.69	< .001	-.84	-.41
mMNA	.23	.06	544.54	3.70	< .001	.11	.36
Dementia duration	-.80	.14	274.71	-5.53	< .001	-1.08	-.51
NPI	-.08	.02	480.82	-4.21	< .001	-.12	-.04

Note. Dependent variable: WLM.

Table 8

Linear Mixed Model of mMNA and WLR

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Intercept	17.26	1.81	375.77	9.53	< .001	13.70	20.83
Time (years)	-2.93	.68	276.00	-4.31	< .001	-4.26	-1.59
mMNA	.22	.10	397.74	2.24	.026	.03	.41
Time*mMNA	.13	.04	238.75	3.29	< .001	.05	.21
Dementia duration	-1.02	.16	260.22	-6.42	< .001	-1.33	-.71
Dementia type (compared to other)							
AD	-1.81	.85	268.04		.034	-3.47	-.14
VaD	.09	1.13	256.25	.08	.935	-2.12	2.31
NPI	-.12	.02	504.36	-5.52	< .001	-.17	-.08

Note. Dependent variable: WLR.

($p < .001$). Significant covariates included type of dementia ($p = .02$), dementia duration at baseline ($p < .001$), and NPI ($p < .001$). Compared to individuals with other dementias, individuals with AD had 1.81 points lower scores on WLR ($p = .034$). Each additional year of dementia duration at baseline and point increase on the NPI was associated with 1.02-point and .12-point decreases on the WLR test, respectively. Figure 7 demonstrates these effects for selected values on the mMNA representing scores in the following categories: well-nourished, at risk for malnutrition, and mal-nourished. Covariate values for this plot are based on the sample means: dementia duration of 3.44, diagnosis of AD, and NPI of 8.68.

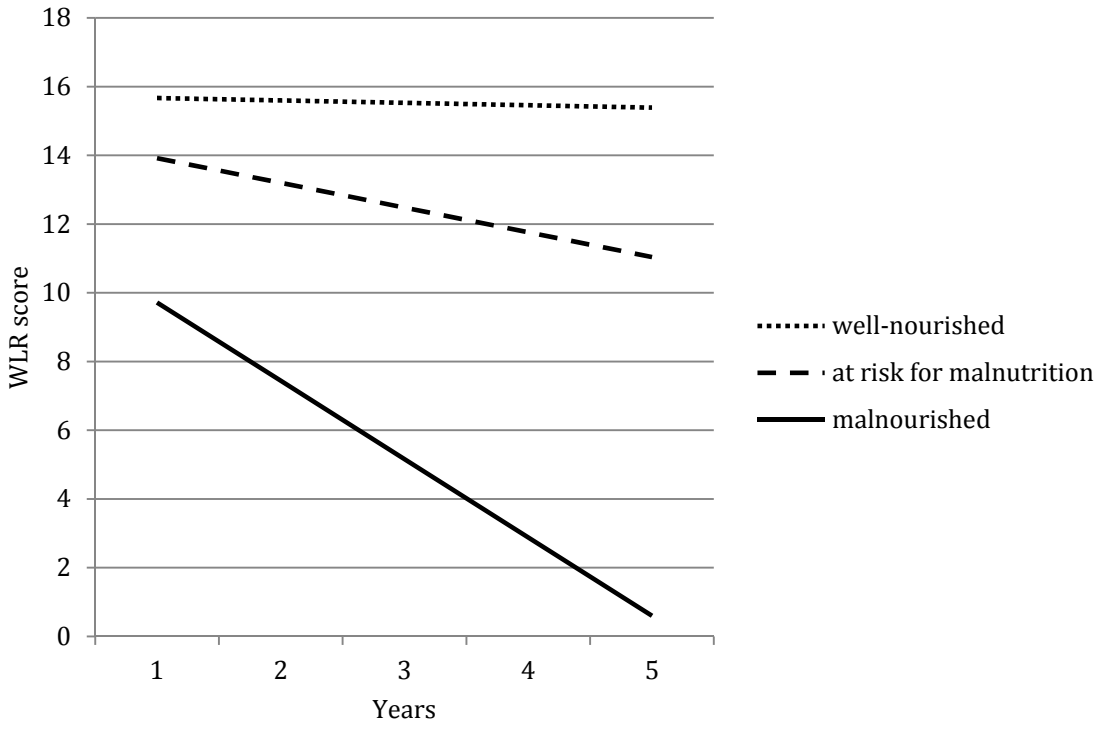

Figure 7. mMNA predicts rate of decline on WLR.

mMNA and Constructional Praxis Recognition Memory

Constructional praxis recognition scores declined linearly over time (β = -.17, p < .001). Testing of a non-linear term for time (time^2) was not significant (β = -.02, p = .213). mMNA significantly predicted overall performance (β = .09, p < .001) but not *rate* of decline (mMNA x time interaction; β = .01, p = .366). With the inclusion of covariates, each additional point on the mMNA was associated with a .08-point increase in constructional praxis score (p < .001; see Table 9). Significant covariates included dementia duration (p < .001), dementia type (p = .012), and NPI (p = .001). Each additional year of dementia duration at baseline and point increase in NPI was associated with .15-point and .02-point decreases in praxis recognition (respectively), while those with AD had .45-point lower praxis recognition scores than those with other forms of dementia (p = .023).

Table 9

Linear Mixed Model of mMNA and Constructional Praxis Recognition

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Upper bound
Intercept	2.32	.38	413.64	6.06	<.001	1.57	3.08
Time (yrs)	-.11	.04	89.84	-3.27	.002	-.19	-.05
mMNA	.08	.02	464.33	3.97	<.001	.04	.12
Dementia Duration	-.15	.04	229.37	-4.26	<.001	-.22	-.08
NPI	-.02	.01	474.25	-3.23	.001	-.03	-.01
Dementia Type (compared to other)							
AD	-.45	.20	241.62	-2.28	.023	-.83	-.06
VaD	.00	.26	224.65	.01	.989	-.50	.51

Note. Dependent variable: Constructional praxis recognition.

mMNA and Expressive Language

In the initial analyses of BNT performance, a measure of expressive language through confrontation naming, negative coefficients for time and time^2 were statistically significant, indicating an accelerating (nonlinear) rate of decline in in this domain. Addition of mMNA scores suggested a statistically significant main effect (β = .35; p < .001), but rate of change indicated by interactions between mMNA with time (p = .805) and time^2 (p = .722) were not statistically significant. mMNA significantly predicted BNT scores even with covariate adjustment (see Table 10), such that each additional point on the mMNA was associated with a .31-point (p < .001) increase on the BNT after controlling for dementia duration (p < .001), type of dementia (p = .011) and NPI (p = .002). Each additional year of dementia duration at baseline and point higher on the NPI was associated with 1.73-point and .06-point

Table 10

Linear Mixed Model of mMNA and BNT

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Upper bound
Intercept	19.59	1.74	453.63	11.23	<.001	16.16	23.01
Time (yrs)	-.58	.24	269.79	-2.38	.018	-1.06	-.10
Time^2	-.11	.05	231.36	-2.15	.032	-.22	-.01
mMNA	.31	.07	382.58	4.16	<.001	.16	.45
Dementia duration	-1.73	.22	251.29	-7.88	<.001	-2.17	-1.30
Dementia Type (compared to other)							
AD	-2.68	1.16	248.63	-2.31	.022	-4.97	-.39
VaD	.22	1.56	244.84	.14	.889	-2.85	3.28
NPI	-.06	.02	316.43	-3.11	.002	-.10	-.02

Note. Dependent variable: BNT.

decreases on the BNT, respectively. Compared to other dementias, AD was associated with a 2.68-point (p = .022) decrease in BNT score.

mMNA and Executive Function

The preliminary stepwise analyses of the CERAD verbal fluency test, a measure of both expressive language and executive functioning, indicated that time (β = -1.09, p < .001) but not time^2 (p = .207) was significant, indicating a linear trajectory of declining scores. Higher mMNA was associated with higher verbal fluency (β = .40, p < .001), but there was no association with rate of change in fluency over time (interaction between mMNA and time was nonsignificant; p = .872). This association between mMNA and fluency remained (β = .34, p < .001) even after holding constant statistically significant covariates, which included dementia duration at baseline (p < .001), gender (p = .016), and NPI (p = .002). Each additional year of dementia duration at visit one was associated with a .6 point decrease on the CERAD verbal fluency test while each point increase on the NPI was associated with a .06 decrease on the verbal fluency test. In addition, males had higher scores on verbal fluency by 1.31 points (p = .016). Table 11 shows final linear mixed model results.

mMNA and Visuospatial Reasoning

Exploratory analyses of the trajectory of constructional praxis scores indicating a non-linear association over time (time^2), which was statistically significant (β = -.03, p = .01). Note that the linear term of time was nonsignificant. mMNA (β = .26, p < .001) was significant but not its interaction with time (p = .58) nor time^2 (p = .76). mMNA

Table 11

Linear Mixed Model of mMNA and Verbal Fluency

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Intercept	6.70	1.21	552.75	5.56	<.001	4.33	9.07
Time (yrs)	-.86	.10	116.59	-8.60	<.001	-1.06	-.66
mMNA	.34	.06	538.76	5.78	<.001	.23	.46
Dementia duration	-.61	.14	264.96	-4.27	<.001	-.89	-.33
NPI	-.06	.02	480.72	-3.14	.002	-.09	-.02
Males	1.31	.54	262.72	2.42	.016	.24	2.37

Note. Dependent variable: Verbal fluency.

score remained significant ($\beta = .23$, $p < .001$) controlling for significant covariates (NPI and dementia duration). For every point increase in NPI score and additional year of dementia duration at baseline, there were associated 0.04-point ($p < .001$) and .41-point ($p < .001$) decreases in the constructional praxis test, respectively. Table 12 shows final linear mixed model results.

Research Question #3: Components of the mMNA and Rate of Cognitive Decline

Carbohydrates and Neuropsychological Functioning

In linear mixed effects models with carbohydrate intake, time, and time^2 as predictors for each neuropsychological test score, frequency of carbohydrate intake was not significantly associated with any of the neuropsychological outcomes in bivariate or multivariate models. Table 13 selectively displays the terms for frequency of

Table 12

Linear Mixed Model of mMNA and Constructional Praxis

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	6.14	.77	425.11	7.94	<.001	4.62	7.66
Time (yrs)	-.12	.14	248.41	-.82	.412	-.40	.16
Time^2	-.06	.03	197.52	-2.03	.044	-.12	.00
mMNA	.23	.04	419.82	5.93	<.001	.16	.31
Dementia duration	-.41	.09	210.32	-4.59	<.001	-.58	-.23
NPI	-.04	.01	332.15	-3.43	.001	-.06	-.02

Note. Dependent variable: dps: CERAD praxis.

Table 13

Carbohydrate Intake estimates From Linear Mixed Model by Neuropsychological Test

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
BNT	-.02	.12	310.87	-.20	.85	-.26	.21
Fluency	-.04	.11	415.55	-.40	.70	-.25	.17
Praxis	.02	.07	316.74	.22	.82	-.12	.15
Praxis recognition	.02	.04	405.14	.46	.65	-.05	.09
Word list memory	-.11	.11	420.71	-.97	.33	-.33	.11
Word list recognition	-.06	.13	393.47	-.47	.64	-.33	.20

Note. All models controlled for time (yrs) while BNT and Praxis also controlled for time^2 (yrs^2).

carbohydrate intake for each of the neuropsychological tests.

Protein and Neuropsychological Functioning

In linear mixed effects models with protein intake, time, and time^2 as predictors for each neuropsychological test score, frequency of protein intake was significantly

associated with WLM but no other test outcome (see Table 14 for summary of nonsignificant results). In this domain, greater protein intake was associated with *worse* overall WLM (β = -.36, p = .004) scores, but not with rate of change (p = .515). This effect was marginally significant after controlling for significant covariates (see Table 15), with each additional occasion of daily protein consumption predicting .23 fewer points on the WLM (p = .061). Significant covariates included dementia duration (p < .001), NPI score (p < .001), and place of residence (p < .001). Each additional year of dementia duration at baseline and point increase on the NPI was associated with .69-point and .10-point decreases on WLM, respectively, while those who were living at home and in assisted living facilities scored higher on the WLM than those who were living in nursing homes. Place of residence was tested in the model due to its strong association with protein intake. BMI was also tested but did not significantly improve model fit after accounting for place of residence. This analysis was investigated further by stratifying animal and plant protein.

Table 14

Protein Intake estimates from Linear Mixed Model by Neuropsychological Test

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
BNT	-.12	.12	281.87	-.96	.338	-.37	.13
Fluency	-.13	.11	389.42	-1.18	.239	-.34	.09
Praxis	.03	.06	251.41	.48	.630	-.09	.15
Praxis Recognition	-.04	.03	486.71	-1.30	.194	-.11	.02
Word List Recognition	-.16	.15	395.17	-1.12	.263	-.45	.12

Note. All models controlled for time (yrs) while BNT and Praxis also controlled for time^2 (yrs^2).

Table 15

Linear Mixed Model of Protein and WLM

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	10.47	1.03	513.75	10.12	.000	8.44	12.50
Time (yrs)	-.59	.11	116.68	-5.48	.000	-.81	-.38
Protein	-.23	.12	452.99	-1.88	.061	-.47	.01
Dementia duration	-.69	.14	282.15	-4.89	.000	-.96	-.41
NPI	-.10	.02	519.05	-5.11	.000	-.14	-.06
Residence (compared to nursing home)							
Home	3.78	.72	468.88	5.22	.000	2.36	5.20
Assisted Living	2.26	.80	496.39	2.81	.005	.68	3.83

Note. Dependent variable: WLM.

Intake of protein from plant sources was not predictive of overall WLM score (p = .517) or rate of change in WLM score over time (p = .536). Intake of protein from animal sources was significantly associated with overall WLM score (β = -.38, p = .003) but not with rate of WLM decline over time (p = .462). Holding significant covariates constant, each additional occasion of daily protein consumption from animal sources was associated with a .23-point decrease on WLM (p = .068), though the effect held marginal statistical significance. Covariates included dementia duration (β = -.72, p < .001), NPI (β = -.09, p < .001), and place of residence (p < .001) such that those with longer dementia duration and higher NPI performed worse on WLM while those living at home (β = 3.26, p < .001) or in assisted living facilities (β = 1.80, p = .02) had higher WLM scores compared to those in nursing homes. Similar to the composite protein model previously described, BMI was statistically significant until place of residence was accounted for. Table 16 shows results of linear mixed models.

Table 16

Linear Mixed Model of Animal Protein and WLM

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	11.03	1.03	538.95	10.74	.000	9.01	13.05
Time	-.61	.11	114.41	-5.75	.000	-.82	-.40
Animal protein	-.23	.13	456.01	-1.83	.068	-.49	.02
Dementia duration	-.72	.14	284.13	-5.11	.000	-1.00	-.44
NPI	-.09	.02	521.59	-4.81	.000	-.13	-.05
Residence (compared to nursing home)							
Home	3.26	.71	492.75	4.60	.000	1.87	4.66
Assisted living	1.80	.77	524.07	2.33	.020	.28	3.32

Note. Dependent variable: WLM.

Fruit/Vegetables and Neuropsychological Functioning

Consumption of fruit and vegetables was not significantly associated with any measure of neuropsychological performance except constructional praxis (see Table 17 for summary of nonsignificant results of models controlling for time and time^2). Previous analyses indicated that constructional praxis was best modeled non-linearly with time^2; therefore, the base model included time and time^2 as covariates. Daily fruit consumption significantly predicted constructional praxis performance ($\beta = -.21$, $p = .047$) in a model including significant covariates (dementia duration, NPI, and BMI). Every additional year of dementia duration and point on the NPI was associated with .42-point ($p < .001$) and .05-point ($p < .001$) decreases in praxis scores while each point increase in BMI was associated with a .09-point ($p = .004$) increase in praxis score. Table 18 shows linear mixed model results.

Table 17

Fruit/Vegetable Intake estimates from Linear Mixed Model by Neuropsychological Test

						95% confidence interval	
Dependent variable	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
BNT	.13	.18	306.51	.72	.473	-.23	.50
Fluency	-.19	.16	433.89	-1.18	.240	-.52	.13
Praxis recognition	.06	.06	423.24	.99	.322	-.05	.17
Word list memory	-.12	.17	436.89	-.69	.492	-.46	.22
Word list recognition	.03	.21	369.49	.15	.881	-.37	.44

[a]All models controlled for time (yrs) while BNT also controlled for time^2 (yrs^2).

Table 18

Linear Mixed Model of Fruit and Constructional Praxis

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
Intercept	8.45	.91	373.73	9.28	.000	6.66	10.24
Time (yrs)	-.17	.15	258.68	-1.14	.256	-.46	.12
Time^2	-.08	.03	210.22	-2.48	.014	-.14	-.02
Fruit	-.21	.11	341.24	-1.99	.047	-.43	.00
Dementia duration	-.42	.09	212.11	-4.73	.000	-.60	-.25
NPI	-.05	.01	374.29	-3.86	.000	-.07	-.02
BMI	.09	.03	386.31	2.87	.004	.03	.15

Note. Dependent variable: Constructional praxis.

Protein/Carbohydrate Pattern and Neuropsychological Functioning

While the baseline distribution of daily carbohydrate and protein intake used in the moderation method was previously discussed, frequencies of each group used in the categorical estimation can be found in Table 19.

Table 19

Frequency of Protein-Carb Patterns

Protein-carb pattern	Frequency	Percent
All others	117	49.0
High protein, high carb	47	19.7
High protein, low carb	24	10.0
Low protein, low carb	34	14.2
Low protein, high carb	17	7.1
Total	239	100.0

Linear mixed effects models tested the pattern of protein and carbohydrate intake with neuropsychological performance by modeling these categorical and moderation terms independently as well as their interactions with time. The only statistically significant effect was found between the categorical assessment of protein/carbohydrate intake and WLM using low protein-high carbohydrate as the reference category. The nonsignificant results are presented in Tables 20 and 21.

Protein/Carbohydrate Pattern and WLM

Linear mixed effect models estimated the associated between the protein/ carbohydrate patterns of consumption and WLM, showing statistical significance for the categorical method ($p = .002$) for predicting memory performance, but not rate of decline in this area ($p = .144$). In models including covariates, those with high protein/high carb ($p = .002$) and high protein/low carb ($p = .036$) patterns of consumptions had significantly worse WLM scores by 2.22 and 1.56 points, respectively, compared to those with a low protein/high carb pattern of consumption (Table 22). This suggests that a diet

Table 20

Tests of Fixed Effects for Neuropsychological Functioning and Pattern of Protein-Carbohydrate Intake

Dependent variable	Numerator *df*	Denominator *df*	*F*	Sig.
BNT	4	276.678	1.481	.208
Fluency	4	378.79	.763	.550
Praxis	4	276.455	.878	.478
praxis recognition	4	392.300	.618	.650
word list recognition	4	374.651	2.194	.069

Note. Independent variable: Hi-Lo categorical variable.

Table 21

Linear Mixed Models of Neuropsychological Functioning and Interactions between Protein and Carbohydrate Intake

						95% confidence interval	
Dependent variable	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
BNT	.003	.08	286.49	.05	.964	-.16	.16
Fluency	.04	.07	361.67	.60	.550	-.09	.17
Praxis	-.034	.05	284.72	-.81	.420	-.14	.06
Praxis recognition	-.03	.03	385.58	-1.26	.207	-.08	.02
Word list memory	-.08	.08	390.71	-1.01	.313	-.23	.08
Word list recognition	-.04	.09	365.04	-.41	.682	-.22	.14

[a]Independent variable: Interaction between daily carb and protein intake.

high in protein is associated with worse memory performance in persons with dementia. Statistically significant covariates included dementia duration (β = -.80, $p < .001$), NPI (β = -.09, $p < .001$), and BMI (β = .11, $p = .034$).

BMI and Neuropsychological Functioning

Two hundred forty-three participants had mean (*SD*) BMI of 25.59 (4.32) at

Table 22

Linear Mixed Model of Protein/Carb Consumption and WLM

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	11.48	1.55	520.64	7.40	.000	8.43	14.53
Time (yrs)	-.76	.11	111.16	-7.06	.000	-.98	-.55
Protein/carb consumption (compared to lo pro/hi carb)							
All other	-.79	.59	392.84	-1.35	.179	-1.95	.36
Hi pro/hi carb	-2.22	.72	421.22	-3.09	.002	-3.62	-.81
Hi pro/lo carb	-1.56	.74	395.54	-2.11	.036	-3.02	-.10
Lo pro/lo carb	-.63	.70	407.52	-.90	.369	-2.00	.74
Dementia duration	-.80	.15	276.00	-5.49	.000	-1.08	-.51
NPI	-.09	.02	504.31	-4.60	.000	-.13	-.05
BMI	.11	.05	511.30	2.12	.034	.01	.21

Note. Dependent variable: World list memory.

baseline with minimum and maximum values of 13.93 and 42.90. The distribution of BMI scores is presented in Figure 8. In linear mixed models, BMI was investigated as both a continuous and categorical variable to represent underweight, normal weight, overweight, and obese groups. At baseline, there were 10 participants in the underweight group, 99 in the normal weight group, 101 in the overweight group, and 33 in the obese group.

BMI and Memory

BMI was associated with all cognitive tests except for BNT ($p = .191$ for continuous BMI and $p = .777$ for categorical). Higher BMI was associated with higher performance on constructional praxis and delayed memory measures of praxis recognition and word list recognition. There was a similar, but marginally significant,

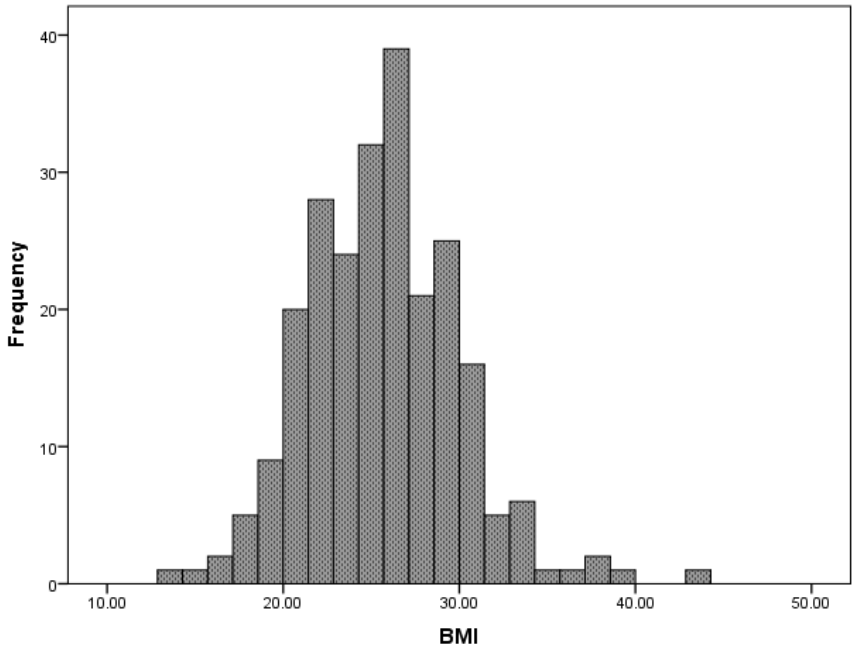

Figure 8. Baseline distribution of BMI.

trend for BMI with word list immediate recall and verbal fluency. Higher BMI was associated with higher scores on praxis recognition (β = .09, p = .004) but not with rate of change (interaction with time p = .686). The association remained significant after the addition of covariates, and for each unit increase of BMI, there was a .05-point increase on praxis recognition score (p = .001; Table 23). Statistically significant covariates included dementia duration (p < .001), dementia type (p = .016), and NPI (p < .001). Every additional year of dementia duration and point on the NPI was associated with .17 and .02-point decreases on praxis recognition scores, respectively. Compared to the other dementias, individuals with AD performed worse by .34 points. This effect was also demonstrated when BMI was analyzed categorically (p = .038; see Table 24) to indicate that those in the underweight (β = -.62, p = .054) and normal weight (β = -.32, p = .059) groups had worse scores than those in the obese group.

Table 23

Linear Mixed Model of BMI and Praxis Recognition

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	2.41	.40	328.29	5.96	<.001	1.61	3.20
Time (yrs)	-.13	.03	81.36	-3.85	<.001	-.20	-.06
BMI	.05	.01	363.33	3.49	.001	.02	.08
Dementia duration	-.17	.03	237.85	-4.97	<.001	-.24	-.10
Dementia type (compared to other)							
AD	-.34	.19	242.03	-1.79	.075	-.72	.03
VaD	.16	.25	224.77	.63	.530	-.34	.66
NPI	-.02	.01	493.48	-3.93	<.001	-.03	-.01

Note. Dependent variable: Constructional praxis recognition.

Table 24

Linear Mixed Model of Categorical BMI and Praxis Recognition

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	3.82	.26	341.69	14.88	.000	3.31	4.32
Time (yrs)	-.13	.03	82.00	-3.72	.000	-.20	-.06
BMI (compared to obese)							
Underweight	-.62	.32	425.32	-1.93	.054	-1.24	.01
Normal	-.32	.17	490.21	-1.89	.059	-.64	.01
Overweight	-.05	.15	460.32	-.31	.757	-.35	.25
Dementia duration	-.17	.03	236.44	-5.01	.000	-.24	-.11
Dementia type							
AD	-.33	.19	243.22	-1.71	.088	-.71	.05
VaD	.16	.25	224.13	.64	.520	-.34	.66
Other	.00[b]	.00	.	.	.	.	.
NPI	-.02	.01	492.95	-3.92	.000	-.03	-.01

Note. Dependent variable: Constructional praxis.

Higher BMI was associated with better performance in word list memory delayed recognition testing (β = .13, p = .037) but not *rate* of performance change over time (BMI*time; p = .692). However, neither categorical BMI (p = .942) nor its interaction with time (p = .134) was significantly associated with WLR. Controlling for confounding factors, each unit increase in BMI was associated with a .12-point increase on WLR (p = .031). Covariates included dementia duration at baseline (p < .001), dementia type (p = .028), and NPI (p < .001) in the final model. Every additional year of dementia duration and point on the NPI was associated with 1.07 and .13-point decreases on WLR scores, respectively. Compared to the other dementias, individuals with AD performed worse by 1.39 points. See Table 25 for model results for WLR.

BMI was initially positively associated with word list memory immediate recall; however, this was marginally significant (β = .10, p = .056) and became less so after significant covariates (dementia duration at baseline and NPI) were included in the final

Table 25

Linear Mixed Model of BMI and WLR

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
Intercept	17.65	1.69	399.75	10.42	<.001	14.32	20.97
Time (yrs)	-.96	.13	68.98	-7.67	<.001	-1.21	-.71
BMI	.12	.06	451.05	2.16	.031	.01	.24
Dementia duration	-1.07	.16	261.86	-6.83	<.001	-1.38	-.76
NPI	-.13	.02	536.28	-5.75	<.001	-.17	-.09
Dementia type (compared to other)							
AD	-1.39	.84	269.26	-1.65	.101	-3.04	.27
VaD	.71	1.12	258.50	.63	.527	-1.50	2.93

Note. Dependent variable: Word list recognition.

model (p = .083). Furthermore, investigation of categorical BMI produced highly nonsignificant results for its association with WLM (p = .426). See Table 26 for complete model description of the former.

BMI and Expressive Language/Executive Functioning

In initial linear mixed models, BMI was associated with verbal fluency performance (β = .10, p = .042), but not rate of decline (p = .981). This relationship between BMI and verbal fluency was weakened to marginal significance (β = .09, p = .063) after inclusion of covariates but indicated a trend for higher BMI to predict higher performance in this cognitive domain (Table 27); however, investigation of categorical BMI demonstrated highly nonsignificant results (p = .281). Covariates for the former model included dementia duration (β = -.68, p < .001), gender (β = 1.66, p = .003), and NPI (β = -.06, p = .001). While those who had longer dementia duration and higher behavioral disturbances did worse in verbal expression, males performed significantly better than females.

Table 26

Linear Mixed Model of BMI and WLM

						95% confidence interval	
Parameter	Estimate	Std. error	*df*	*t*	Sig.	Lower bound	Lower bound
Intercept	11.17	1.42	496.94	7.88	<.001	8.38	13.95
Time (yrs)	-.71	.11	106.69	-6.66	<.001	-.92	-.50
BMI	.09	.05	532.94	1.74	.083	-.01	.19
Dementia duration	-.85	.14	278.22	-5.88	<.001	-1.13	-.56
NPI	-.09	.02	514.27	-4.72	<.001	-.13	-.05

Note. Dependent variable: Word list memory.

Table 27

Linear Mixed Model of BMI and Verbal Fluency

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	10.12	1.45	490.24	7.00	<.001	7.28	12.96
Time (yrs)	-.98	.10	114.83	-9.65	<.001	-1.18	-.78
BMI	.09	.05	541.16	1.87	.063	.00	.19
Dementia Duration	-.68	.15	267.59	-4.54	<.001	-.97	-.38
Males	1.66	.56	261.87	2.95	.003	.55	2.77
NPI	-.06	.02	475.33	-3.42	.001	-.10	-.03

Note. Dependent variable: CERAD verbal fluency.

BMI and Visuospatial Skills

Previous modeling of constructional praxis demonstrated that a non-linear trajectory was the best fit, thus BMI was added to the base model of time and time^2. Higher BMI was associated with better performance in praxis ($\beta = .09$, $p = .004$) but not *rate* of decline as tested by interaction with both time ($\beta = .03$, $p = .784$) and time^2 ($\beta = .01$, $p = .80$). BMI remained significant after inclusion of covariates ($p = .003$) with each additional point in BMI predicting .09-point increase in praxis score. Statistically significant covariates include dementia duration ($\beta = -.45$, $p < .001$) and NPI ($\beta = -.04$, $p < .001$), suggesting that those who had longer dementia duration and more severe behavioral disturbances had worse visuospatial skills. These effects were refined further with analysis of categorical BMI ($p = .003$) to show that those in the normal weight group had worse scores on praxis than those in the obese group ($\beta = -1.10$, $p = .001$). Tables 28 and 29 show final linear mixed model results.

Table 28

Linear Mixed Model of BMI and Constructional Praxis

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	7.86	.87	350.82	9.05	<.001	6.15	9.57
Time (yrs)	-.15	.15	245.19	-1.03	.306	-.44	.14
Time^2 (yrs^2)	-.07	.03	202.76	-2.30	.022	-.14	-.01
BMI	.09	.03	378.41	2.96	.003	.03	.15
Dementia duration	-.45	.09	207.21	-4.97	<.001	-.63	-.27
NPI	-.04	.01	343.44	-3.80	<.001	-.07	-.02

Note. Dependent variable: CERAD constructional praxis.

Table 29

Linear Mixed Model of Categorical BMI and Constructional Praxis

Parameter	Estimate	Std. error	*df*	*t*	Sig.	95% confidence interval	
						Lower bound	Lower bound
Intercept	10.94	.44	341.97	24.98	.000	10.08	11.80
Time (yrs)	-.12	.15	246.14	-.83	.410	-.41	.17
Time^2 (yrs^2)	-.08	.03	200.74	-2.52	.012	-.14	-.02
BMI (compared to obese)							
Underweight	-1.32	.74	430.94	-1.80	.073	-2.77	.12
Normal	-1.10	.34	383.24	-3.28	.001	-1.76	-.44
Overweight	-.38	.28	292.76	-1.34	.182	-.94	.18
Dementia duration	-.46	.09	210.82	-5.08	.000	-.64	-.28
NPI	-.04	.01	338.67	-3.79	.000	-.07	-.02

Note. Dependent variable: Constructional praxis.

CHAPTER V

DISCUSSION

This investigation from a population-based, longitudinal study of persons with dementia in Cache County, Utah, explored the relationship between nutritional status and selected components with neuropsychological functioning. The following results were obtained: (a) nutritional status declined over time and was associated with performance in memory, executive functioning, visuospatial skills, and verbal fluency; (b) overall consumption of carbohydrates, fruit, and vegetables declined slightly over time; and (c) particular components of nutritional status were differentially associated with neuropsychological performance. Each section will be described in greater detail in the following discussion. Finally, strengths and limitations of the study as well as future directions for research will be discussed.

Nutritional Status: Change over the Course of Dementia

Overall, nutritional status declined over the course of the study as indicated by an approximate 1/4-point loss on the mMNA each year. This decline, however, was accounted for by increasing dementia severity. Others have also found that nutritional status declines over time (Cortes et al., 2008) in dementia samples, and is associated with dementia severity (Cortes et al., 2008; Malara et al., 2014; Roque, Salva, & Vellas, 2013). For example, Cortes and colleagues found that nutritional status declined linearly in persons with AD, as evidenced by a mean loss of approximately .4-points each year in a two-year follow-up of a cohort of 349 French individuals with AD. When stratified by

dementia severity, those with moderately severe dementia experienced double the loss of nutritional status compared to mild cases (Cortes et al., 2008). While a direct comparison between the current study results and the French sample cannot be made due to the changes in the mMNA employed here, a ratio comparison suggests that the mild cases in the French cohort experienced approximately the same loss in nutritional status as the overall loss in the present study. Cortes et al. used the MMSE to capture dementia severity while the present study used CDR-sb in modeling trajectory of nutritional status so this could account for some differences. Also, the present sample may be experiencing less severe symptoms overall. It has been documented that females and those who acquire dementia at a younger age progress more quickly (Agüero-Torres, Fratiglioni, & Winblad, 1998; Sona, Ellis, & Ames, 2013; Tschanz et al., 2011). Whereas, the French sample was about a decade younger at baseline, comprised of 71% females (vs DPS = 52%), and identified through an AD clinic (which generally attracts persons already experiencing more severe symptoms), the Cache County sample was population-based and consisted of incident dementia cases, therefore likely identifying those at earlier stages of the condition. The French sample also consisted of those with AD only. Since dementia severity predicts nutritional status and is a confounding item of the original MNA, it is possible that the more profound nutritional loss experienced by French sample was a reflection of a more severe sample.

With respect to other factors predicting nutritional status, those who acquired dementia at a later age had worse nutritional status as did those who did not reside with their caregivers. Women were less represented in the well-nourished group at baseline

and were at greater risk for worse nutritional status over the period of observation compared to men. In addition, those who were diagnosed with AD or VaD had significantly better nutritional status than those were diagnosed with another form of dementia.

The present associations of nutritional status with age (Guerin et al, 2005; Roque et al., 2013; Vellas et al., 2005) and gender (Vellas et al., 2005) have been suggested in the literature; however, the present study expanded upon previous results with longer follow-up times and studied a population-based (rather than clinic-based) sample of persons with all-cause dementia. The protective effects of caregiver co-residence and dementia type for nutritional status have not been previously examined as the majority of studies sampled participants with primarily AD type dementia and did not examine the effects of caregiver coresidence.

Daily consumption of carbohydrates (bread, sweets, cereal), protein, fruit, and vegetables decreased over the course of the study, though the effects were small, amounting to a reduction in the frequency of consumption that was less than a daily serving per year. For example, an individual who consumed "carbohydrate" foods five times per day would consume these foods only four times per day 10 years later. These results complement previous findings, which suggest that weight loss (presumably a result of decreased intake and meal complexity) is a common correlate of the onset of AD and other dementias (Albanese 2013; Barrett-Connor et al., 1996; Guerin et al. 2005; White et al., 1996). Interestingly, longer dementia duration was significantly associated with higher carbohydrate consumption, suggesting those who were further along in the

progression of the disease increased their preference for carbohydrates. There was also a significant decrease in protein consumption, especially for those living at home compared to those living in nursing home. This result may indicate that individuals living at home are perhaps living alone and neglecting their dietary needs while individuals living in nursing homes are monitored for eating more balanced meals. Perhaps meals consisting primarily of protein are more difficult to prepare and therefore avoided among independently living participants. Alternatively, place of residence may be a reflection of dementia severity, suggesting that higher protein intake may be a marker of dementia severity; however, when tested together, place of residence better accounted for the variance in protein intake. It should also be noted that the measures of food consumption for this study were crude, limiting the investigation to frequency of intake rather than quantity. Thus it is difficult to determine whether the participants would have met the US Department of Agriculture criteria for nutrient intake (e.g., 5-5.5 oz of protein or 3 cups of dairy items daily; U.S. Department of Agriculture, 2015).

Nutritional Status and Neuropsychological Function

While the current state of the literature indicates that worse nutritional status is associated with worse cognitive status in persons with dementia (Cortes et al., 2008; Guerin et al, 2005; Malara et al., 2013; Roque et al., 2013; Vellas et al., 2005), these findings have been based on the MMSE, a global measure of cognitive capacity, rather than tests of specific neuropsychological domains. Findings from the current study suggested that higher scores on the mMNA were associated with better performance in

verbal expression, visuospatial skills, executive functioning, and memory (immediate recall and delayed recognition) over annual follow-ups for as long as 5.92 years. Furthermore, nutritional status predicted *rate* of decline on a delayed recognition memory task. Therefore, better nutritional status not only predicted better functioning in all cognitive domains but also predicted slower *rate* of decline in memory. Based on the annual change scores on these neuropsychological tests in a cohort with probable AD as outlined in J. C. Morris and colleagues (1993), cognitive decline occurs rapidly and at a magnitude of .3-points (word list recall) to 2-points (word list memory and BNT) loss per year. Nutritional status accounts for a significant amount of this loss and may alter the trajectory for some. This is an important observation as maintenance of cognitive capacity may prolong independence in persons progressing through dementia, thereby increasing quality of life for individuals diagnosed with the condition and decreasing burden (financial and otherwise) on caregivers and institutional resources. Though the modification of cognitive ability with nutritional status to predict such outcomes is not well-explored, in other analyses with the Cache County sample found that better nutritional status does predict better functional ability in persons with dementia (Sanders et al., 2013). Other research of persons aged 60 and older without dementia suggests that nutritional wellbeing is associated with higher quality of life (American Dietetic Association [ADA], 2005).

Components of the mMNA and Cognitive Decline

Of the specific nutrition-related components of the mMNA that were investigated

in the current study, significant effects and trends were predominately found for BMI predicting decline in almost all tests of neuropsychological function. Higher BMI significantly predicted higher scores in visuospatial skills and delayed memory recognition (verbal and visual), and was marginally associated with higher immediate memory recall and verbal expression. With the mean BMI scores of the group hovering over the healthy/overweight boundary of 25, it was hypothesized that a BMI representative of this weight range may be critical for performance on delayed recall and visuospatial tasks; however, when BMI was investigated categorically, those who were in the low and normal weight ranges had significantly worse performance in visuospatial construction and memory tasks compared to obese individuals. This finding compliments the established trend in the literature that weight loss immediately before and during onset of dementia is associated with worse outcomes (Albanese et al., 2013; Barrett-Connor et al., 1996; Guerin et al., 2005; White et al., 1996); however, the seemingly protective effect of an extremely high BMI should be interpreted cautiously as the numbers of underweight and obese individuals were low. While high midlife BMI has been associated with increased risk for dementia and MCI (Kivipelto et al., 2005; Rosengren et al., 2005), the results of the present study indicate a higher late-life BMI may be related to better cognitive functioning in persons who already have dementia. A higher late life BMI may be associated with less frailty and better overall health. Since previous research with this cohort has demonstrated that better overall health predicts higher cognitive function (Leoutsakos et al., 2012), this was controlled for in the models but not found to independently contribute to functioning in these specific

neuropsychological domains beyond what was already captured in diet or BMI.

In a similar theoretical approach to Roberts and colleagues (2012b), the current study investigated the role of the pattern of carbohydrates and protein intake in the diet in addition to analyzing these food groups separately; however, the results contrasted from the findings of Roberts and colleagues, which found that individuals with a high percentage of energy from fats and proteins were at a reduced risk for MCI and dementia compared to individuals with a high percentage of energy intake from carbohydrates. In the present study, the interaction effect between daily carbohydrate and protein intake was nonsignificant for all cognitive outcomes. However, stratification of carbohydrate and protein consumption patterns suggested that a diet comprised of high protein, regardless of level of carbohydrate intake, was associated with worse acquisition of information compared to a diet that was low in protein and high in carbohydrates. While carbohydrate intake alone did not predict cognitive decline, higher consumption protein (especially from animal sources) confirmed this association with worse immediate memory performance. Since the participants of the current study acquired most of their protein through animal sources, it is possible that protein intake also represented high intake of animal fat and potentially a marker of a cardiovascular health, even though overall health was tested. In order to investigate this possibility, BMI was tested as a covariate but became nonsignificant once place of residence was accounted for, indicating that those who live at home had better memory. The relationship between high protein consumption and memory remained, despite these controls. Based on findings from Roberts and colleagues, it would be expected that of the individuals with high

protein intake, those also high in carbohydrates would perform worse than those with high protein/low carbs. Models from the current study suggest that those who had high protein/high carb diets scored about ¾ of a point lower on the memory test than those with high protein/low carb diets; however, separate analyses would need to confirm that this trend is a clinically meaningful difference.

Last, fruit and vegetable consumption significantly predicted neuropsychological status in constructional praxis only, such that higher fruit and vegetable consumption predicted worse visuospatial function. This result may be surprising given the vast literature that documents the protective effects of anti-oxidants (Morris, 2012) and diets rich in fruits and vegetables (Engelhart et al., 2002; Scarmeas et al., 2006) in cognitive health. The protective effect of anti-oxidants through supplement use (Wengreen et al., 2007) and diet (Wengreen et al., 2009) for global cognitive health has even been demonstrated previously in persons without dementia in the larger Cache County cohort. It is possible that the specific neuropsychological domains studied here are representing somewhat different constructs than global cognitive functioning or more likely that the measure of fruit and vegetable intake used for the present study (one question on a nutrition questionnaire) was not sensitive to these effects. Furthermore, the studies in persons without dementia also controlled for other health factors, which can be important moderators of dementia progression (Leoutsakos et al., 2012). Previous research also has found that only 48% of fruit and 25% of vegetables in the fruit/vegetable intake of persons aged 65 and older are the types of fruit and vegetables associated with reduced health risks (ADA, 2005); it may be the case that the present cohort was not eating those

fruits and vegetables with these beneficial qualities.

Strengths and Limitations

This study has the advantage of using longitudinal data from a population-based design, which allows for naturalistic observations of the effects of aging and dementia compared to the possibility of biased sampling of high-risk individuals in a clinic-based design. Multiple observations with high participation rates over the span of 6 years allows for time-varying estimations of the contributing factors in the progression of dementia symptoms. The extent of follow-up conducted in this study is a unique and notable strength compared to previous studies. A consequence, however, of studying older adults with dementia for several years is the increased potential for missing data due to failing health, severe cognitive impairment, and death. This may bias the results to favor a particular gender, place of residence, age, dementia severity, dementia duration, neuropsychiatric symptoms, and nutritional status. Nevertheless, the use of linear mixed models addresses missing data, allowing for inclusion of participant data at any point of observation. Furthermore, most dropouts were due to death rather than refusals and as the median life expectancy in Cache County exceeds the general population by 10-12 years (Murray, 1998), there was the possibility for longer follow-up than other studies. Though presence of dementia typically diminishes life span, the present study followed individuals with incident (therefore, likely less severe at identification) dementia cases, which may have also contributed to exceptional follow-up.

Study weaknesses include use of a homogenous group of mostly middle class,

white, predominately LDS persons residing in a semi-rural community. The LDS community proscribes to lifestyle patterns (no alcohol or tobacco) that may increase longevity and decrease health problems. Some may extend this logic and speculate that people within this community adhere to healthier dietary patterns than the general population or there may be differences in dietary patterns between those residing in rural vs. urban settings. In other work, rates of cardiovascular conditions and diseases in the Cache County cohort were generally similar to those of other populations (Hayden et al., 2006). Research suggests that only 32% of American men and women meet the suggested criteria for fruit and vegetable intake (5 servings/day; ADA, 2005), a finding that is at least consistent with baseline intake in this sample (see Figure 4). Due to the relatively homogeneous sample, it is possible that the findings in the present analysis may not generalize to those of other dementia samples. However, in general, results of the mMNA are broadly consistent with those of others (Cortes et al., 2008; Guerin et al, 2005; Malara et al., 2014; Roque et al., 2013; Vellas et al., 2005). An additional limitation is the inclusion of all-cause dementia cases, which may not capture disease-specific trends; however, dementia type was accounted for in the models. Finally, the modified version of the MNA used in this study excluded some items such as presence of dementia, neuropsychological symptoms, and self-view of nutritional status since these variables confound the outcome measures of cognitive functioning. The psychometric properties of this modified version have not been established and direct comparisons with the original MNA may not be meaningful. Furthermore, due to the lack of validation studies, it is uncertain whether the construct measured by the mMNA represents nutritional status as

operationalized by Guigoz and colleagues (1994).

Future Research

In order to further our understanding of the relationship between nutritional status and dementia progression, it would be beneficial to study the association between nutritional status and neuropsychiatric symptoms over many years of follow-up, especially since these behavioral symptoms tend to vary over time. Furthermore, investigation of the relationship between nutritional status and indicators of independence (e.g., functional measures of ADL and IADL) as well as burden (caregiver stress and cost) would be essential to extend and support the premise of this study. Specifically, examination of the effects of nutritional status and cognitive function in predicting ADL function or the effects of nutritional status and health in predicting ADL function may reveal possible underlying mechanisms. To further our understanding of nutrient factors in relation to dementia outcomes, it would be of interest if future research investigates the relationship between consumption patterns of macronutrients and cognitive, functional, and neuropsychiatric symptoms in persons with dementia. Optimally, an estimation method of energy intake from each nutrient similar to that used by Roberts and colleagues (2012b) could be employed and captured over time for greater specificity and potential for time-varying analyses. As there are many avenues for research of nutritional factors in healthy aging, the suggestions presented here are merely logical first steps in this particular line of research following the results of the current study.

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APPENDICES

Appendix A

Modified Mini-Nutritional Assessment

Table A1

Modified Mini-Nutritional Assessment

mMNA item	DPS item	Values	DPS questionnaire	Source of information
A. Food intake decrease over last 3 mos	Has food intake declined since last visit?	0 'SOME decrease in food intake' 2 'no decrease in food intake'	Nutritional assessment	Caregiver
B. Weight loss over last 3 mos	Weight loss since last visit	0 'some weight loss' 1 'unknown' 3 'no weight loss'	NPI	Caregiver
C. Mobility	Mobility	0 'bed or chair bound' 1 'ambulates with assistance' 2 'ambulates within residence'	ADA	Caregiver
D. Psychological distress/acute disease	N/A			
E. Neuropsychological problems	N/A			
F. BMI	BMI	0 'BMI less than 19' 1 'BMI 19 to less than 21' 2 'BMI 21 to less than 23' 3 'BMI 23 or greater'	MEdHx, general health and neurological exam	Nurse
G. Lives independently	Lives Independently	1 'yes' 0 'no'	GMHR	Nurse
H. Takes >3 prescription drugs per day	Takes more than 3 prescription drugs per day	1 'yes' 0 'no'	Medication inventory	Research staff
I. Pressure sores/Skin ulcers	N/A			
J. Number of full meals/day	# of full meals/day	0 'one meal' 1 'two meals' 2 'three meals'	Nutritional assessment	Caregiver
K. Protein intake/day	Consumption of Protein (composite of dairy, legumes, & meat)	0.0 '0 or 1 yes' 0.5 '2 yes' 1.0 '3 yes'	Nutritional assessment	Caregiver

(*table continues*)

mMNA item	DPS item	Values	DPS questionnaire	Source of information
L. Consumes 2 or more servings of fruit or vegetables per day	Consumes 2 or more servings of fruit or vegetables per day	1 'yes' 0 'no'	Nutritional assessment	Caregiver
M. Fluid intake/day	Consumption of fluid daily	0.0 'less than 3 cups' 0.5 '3 to 5 cups' 1.0 'more than 5 cups'	Nutritional assessment	Caregiver
N. Mode of feeding	Mode of Feeding	0 'unable to eat without assistance' 1 'self-fed with some difficulty' 2 'self-fed without any problem'	ADA	Caregiver
O. Self-view of nutritional status	N/A			
P. Peer comparison of health status	Health Status	0.0 'poor' 0.5 'fair or unknown' 1.0 'good' 2.0 'excellent'	GMHR	Nurse
Q. Mid-arm circumference	Mid-arm Circumference	0.0 'less than 21 cm' 0.5 '21 to 22 cm' 1.0 '22 or greater'	Blood pressure	Nurse
R. Calf circumference	N/A			
Total points possible:		22		

Appendix B

Nutritional Assessment

J1. Since the last visit, has (NAME's) food intake declined due to loss of appetite, digestive problems, chewing or swallowing difficulties?	NO....0 YES, DUE TO LOSS OF APPETITE....1 YES, DUE TO DIGESTIVE PROBLEMS....2 YES, DUE TO DIFFICULTIES IN CHEWING AND SWALLOWING....3 DK....8
J2. How would you describe (NAME's) appetite lately? Would you say (NAME's) appetite is usually very good, good, fair, poor, or very poor?	VERY GOOD....1 GOOD....2 FAIR....3 POOR....4 VERY POOR....5 DK....8
J3. How often per day does (NAME) usually eat a meal?	AT LEAST 3 TIMES EACH DAY....1 AT LEAST 3 TIMES A DAY, 5 OR 6 DAYS A WEEK....2 AT LEAST 3 TIMES EACH DAY, 3 OR 4 DAYS A WEEK....3 TWO TIMES EACH DAY....4 LESS THAN 2 TIMES EACH DAY....5 DK....8
The next few questions are about (NAME's) frequency of consumption of meals and foods. For each question please tell me how often during the past year, on average, (NAME) has eaten the foods listed.	
#1 INTERVIEWER CHECKPOINT: CAN INFORMANT GIVE A GOOD HISTORY OF FOOD CONSUMPTION?	YES (GO TO J4.)....1 NO (GO TO #1a)....0
1a.	INFORMATION PROVIDED BY N.H.....1 INFORMATION PROVIDED ON MENU SHEETS....2 INFORMATION NOT AVAILABLE (GO TO NEXT J14)....3
J4. How often does (NAME) usually eat fruits or vegetables (canned, fresh, frozen, or juice)?	SIX OR MORE TIMES A DAY....1 FOUR OR 5 TIMES A DAY....2 TWO OR 3 TIMES A DAY....3 ONE TIME A DAY....4 FIVE TO 6 TIMES A WEEK....5 TWO TO 4 TIMES A WEEK....6 ONE TIME A WEEK....7 ONE TO 3 TIMES A MONTH....8 NONE OR LESS THAN 1 TIME A MONTH....9 DK....98
J5. How often does (NAME) usually eat cold or cooked cereal, waffles, pancakes, or toast?	SIX OR MORE TIMES A DAY....1 FOUR OR 5 TIMES A DAY....2 TWO OR 3 TIMES A DAY....3 ONE TIME A DAY....4 FIVE TO 6 TIMES A WEEK....5 TWO TO 4 TIMES A WEEK....6 ONE TIME A WEEK....7 ONE TO 3 TIMES A MONTH....8 NONE OR LESS THAN 1 TIME A MONTH....9 DK....98
J6. How often does (NAME) usually eat bread, rolls, rice, pasta, or potatoes?	SIX OR MORE TIMES A DAY....1 FOUR OR 5 TIMES A DAY....2 TWO OR 3 TIMES A DAY....3 ONE TIME A DAY....4 FIVE TO 6 TIMES A WEEK....5 TWO TO 4 TIMES A WEEK....6 ONE TIME A WEEK....7 ONE TO 3 TIMES A MONTH....8 NONE OR LESS THAN 1 TIME A MONTH....9 DK....98

J7. How often does (NAME) usually eat cookies, cakes, pastries, candy or other sweets?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98
J8. How often does (NAME) usually eat meat, eggs, fish, poultry?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98
J9. How often does (NAME) usually eat dried peas, beans, lentils, nuts, or tofu?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98
J10. How often does (NAME) usually drink milk or eat foods made with milk such as cheese, cottage cheese, yogurt, pudding, or ice cream?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98
J11. How often does (NAME) usually drink 1 cup (8 oz) of fluid including water, juice, soft drinks, milk, tea, and coffee?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98
J12. How often does (NAME) drink supplemental or meal replacement beverages such as Ensure or Carnation Instant Breakfast?	SIX OR MORE TIMES A DAY ..... 1 FOUR OR 5 TIMES A DAY ..... 2 TWO OR 3 TIMES A DAY ..... 3 ONE TIME A DAY ..... 4 FIVE TO 6 TIMES A WEEK ..... 5 TWO TO 4 TIMES A WEEK ..... 6 ONE TIME A WEEK ..... 7 ONE TO 3 TIMES A MONTH ..... 8 NONE OR LESS THAN 1 TIME A MONTH ..... 9 DK 98

J13. Is there any other food not mentioned up to now that (NAME) usually eats at least once per day?	YES ..... 1 NO (SKIP TO J14) ..... 0 RF (SKIP TO J14) ..... 7 DK (SKIP TO J14) 8
J13a. What are the additional foods (NAME) eats at least once per day?	FOOD 1. _____ ☐☐☐ FOOD 2: _____ ☐☐☐ FOOD 3: _____ ☐☐☐

Appendix C

Physical Activities Questionnaire

The next questions are about exercise.		
E1.	In the past 12 months, has (NAME) walked for exercise? This includes either walking outside or walking on a treadmill.	YES NO (GO TO E2) RF (GO TO E2) DK (GO TO E2)
a.	In the past 12 months, how many of those months did (NAME) walk for exercise?	MONTHS ☐☐
b.	During those months, how often did (NAME) walk for exercise?	NUMBER OF TIMES ☐☐ PER DAY PER WEEK PER MONTH
c.	What was the average amount of time that (NAME) spent walking per session?	HOURS ☐☐ MINUTES ☐☐
d.	When (NAME) walked for exercise, what was his/her usual pace? Would you say . . .	Casual strolling; from 0 to 2 m.p.h. Average or normal; from 2 to 3 m.p.h. Fairly briskly; from 3 to 4 m.p.h. Briskly or striding more than 4 m.p.h. DK
E2.	In the past 12 months, has (NAME) done heavy housework including vacuuming, mopping or scrubbing floors or sidewalks, moving furniture or boxes?	YES NO (GO TO E3) RF (GO TO E3) DK (GO TO E3)
a.	In the past 12 months, how many of these months has (NAME) done heavy housework?	MONTHS ☐☐
b.	During those months, how often did (NAME) do heavy housework?	NUMBER OF TIMES ☐☐ PER DAY PER WEEK PER MONTH
c.	What is the average amount of time (NAME) spent each time (he/she) did heavy housework?	HOURS ☐☐ MINUTES ☐☐

E3.	In the past 12 months has (NAME) done garden or yard work including weeding, digging, cutting grass <u>while walking</u>, raking or snow shoveling? DO NOT INCLUDE RIDING LAWNMOWER	YES ..... NO (GO TO E4)..... RF (GO TO E4)..... DK (GO TO E4).....
a.	In the past 12 months, <u>how many</u> of these months has (NAME) done garden or yard work?	MONTHS..... ☐☐
b.	During those months, <u>how often</u> did (NAME) do garden or yard work?	NUMBER OF TIMES ..... ☐☐ PER DAY..... PER WEEK..... PER MONTH.....
c.	What is the average amount of time (NAME) spent each time (he/she) did garden or yard work?	HOURS ☐☐ MINUTES ☐☐
E4.	In the past 12 months, has (NAME) used an exercise machine including a treadmill for jogging or running but not walking, an exercise bicycle or some other machine? DO NOT INCLUDE TREADMILL WALKING REPORTED IN E1.	YES ..... NO (GO TO E5)..... RF (GO TO E5)..... DK (GO TO E5).....
a.	In the past 12 months, <u>how many</u> of these months has (NAME) used an exercise machine?	MONTHS..... ☐☐
b.	During those months, <u>how often</u> did (NAME) use an exercise machine?	NUMBER OF TIMES ..... ☐☐ PER DAY..... PER WEEK..... PER MONTH.....
c.	What is the average amount of time (NAME) spent each time (he/she) used an exercise machine?	HOURS ☐☐ MINUTES ☐☐
E5.	In the past 12 months, has (NAME) done calisthenics or lifted weights for exercise?	YES ..... NO (GO TO E6)..... RF (GO TO E6)..... DK (GO TO E6).....

a.	In the past 12 months, <u>how many</u> of these months has (NAME) done calisthenics or lifted weights?	MONTHS ..... ☐☐
b.	During those months, <u>how often</u> did (NAME) do calisthenics or lifted weights?	NUMBER OF TIMES ..... ☐☐ PER DAY ..... PER WEEK ..... PER MONTH .....
c.	What is the average amount of time (NAME) spent each time (he/she) did calisthenics or lifted weights?	HOURS ☐☐ MINUTES ☐☐
E6.	In the past 12 months, has (NAME) done other moderate or vigorous exercise such as swimming laps; aerobics; jogging, running, or bicycling <u>outside</u>; dancing or tennis?	YES ..... NO (GO TO SECTION E7) ..... RF (GO TO SECTION E7) ..... DK (GO TO SECTION E7) .....
a.	In the past 12 months, <u>how many</u> of these months has (NAME) done moderate or vigorous exercise?	MONTHS ..... ☐☐
b.	During those months, <u>how often</u> did (NAME) do moderate or vigorous exercise?	NUMBER OF TIMES ..... ☐☐ PER DAY ..... PER WEEK ..... PER MONTH .....
c.	What is the average amount of time (NAME) spent each time (he/she) did moderate or vigorous exercise?	HOURS ☐☐ MINUTES ☐☐
E7.	<u>Reliability of Informant Report</u> How reliable is the informant's report of the subject?	 VERY RELIABLE ..... PRBLY. REL ..... NOT RELIABLE .....