DIETARY INFLAMMATORY INDEX IN PATIENTS WITH ALZHEIMER'S DEMENTIA COMPARED TO CONTROLS

A Thesis

presented to

the Faculty of the Graduate School

at the University of Missouri-Columbia

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

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JULY 2018

The undersigned, appointed by the Associate Vice Chancellor of the Office of Research and Graduate Studies, have examined the thesis entitled

DIETARY INFLAMMATORY INDEX

IN PATIENTS WITH ALZHEIMER'S DEMENTIA

COMPARED TO CONTROLS

Presented by Allison Kathleen Halt,

A candidate for the degree of master of science,

And hereby certify that, in their opinion, it is worthy of acceptance.

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Professor David Q. Beversdorf

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ACKNOWLEDGEMENTS

It has been, and continues to be, a privilege to work with older adults with dementia. This work would not have been possible without their willingness to participate in research and the unwavering support of their caregivers.

Thank you to my advisor, Dr. David Beversdorf. Thank you for seeing potential in me when I was an undergraduate summer intern in your lab and taking me on as your graduate student. Thank you for trusting me as a first-year graduate student to take on the elderberry clinical trial, which I enjoy immensely. Thank you for your guidance and your support of all my academic endeavors.

Thank you to my committee members, Dr. Zezong Gu and Dr. Dennis Miller, for your insight, guidance, support, and dedication of your time. Thank you to the graduate students and research assistants who came before me and gathered the dietary data analyzed below. Thank you to my lab mates, past and present, who all, in some way, made this project possible.

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LIST OF ABBREVIATIONS

Alzheimer's dementia……AD

Clinical dementia rating……CDR

Dietary inflammatory index……..…....DII

Food frequency questionnaire…….……...…FFQ

Mild cognitive impairment……...……..MCI

Mini Mental Status Exam…….……..MMSE

ABSTRACT

Alzheimer's dementia (AD) is a chronic neurodegenerative disease causing progressive memory loss, cognitive decline across numerous domains, and, eventually, loss of daily living activities. Mild cognitive impairment (MCI) is a significant risk factor for the development of Alzheimer's disease and is believed to be the mildest endpoint on the spectrum of AD. However, not all patients with MCI progress to AD. Understanding individual, modifiable factors influencing differences between MCI and AD can help us understand why some patients progress and others do not. One such well-studied, modifiable factor is diet. The dietary inflammatory index (DII) evaluates various dietary components on how their pro- and anti-inflammatory properties and is a tool that enables us to analyze how pro- or anti-inflammatory an individual's diet is. We found that DII significantly differs between controls, patients with MCI, and patients with AD; controls have the most anti-inflammatory diet and patients with AD having the least anti-inflammatory diet. This evidence supports the crucial role of diet and chronic inflammation in the development and progression of AD.

Dietary Inflammatory Index in Patients with Alzheimer's Dementia Compared to Controls

Alzheimer's disease is a chronic neurodegenerative disease. As the disease progresses, an individual will often develop Alzheimer's dementia (AD) which is characterized by progressive memory loss, cognitive decline across numerous domains, and, eventually, loss of daily living activities. According to the Alzheimer's Association (2018), more than 5.7 million Americans are currently living with AD and, by 2050, that number is projected to rise to 14 million. In addition to an increasing prevalence, Alzheimer's disease also has a dramatically increasing mortality rate. Between 2000 and 2015, deaths from heart disease decreased by 11%, deaths from HIV decreased by 55%, and deaths from AD increased 123%. At this time, there is no cure for AD and treatment options are limited. There are currently two classes of drugs approved by the FDA: cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—and an NMDA receptor blocker—memantine (Casey, Antimisiaris, & O'Brien, 2010). These drugs are merely palliative; they do not alter disease progression. According to Qaseem et al (2008), clinical trials of the aforementioned drugs revealed statistically significant improvement in patients taking cholinesterase inhibitors or memantine; however, the "improvement" may not be clinically important and evidence regarding benefits to quality of life was mixed. Our lack of effective treatments to halt decline is partly due to our lack of full understanding of disease progression.

Understanding the progression of AD begins with early diagnosis, early treatment, and monitoring the course of the dementia. Mild cognitive impairment (MCI) is an intermediary state between normal, age-associated changes in cognition and the more severe cognitive declines associated with dementia. Most researchers and clinicians

assert that MCI is the mildest endpoint on the spectrum of AD (Morris, Storandt, & Miller, 2001) and, in clinical practice, individuals with MCI have a clinical dementia rating (CDR) of 0.5. MCI can be a significant risk factor for the development of AD if Alzheimer's pathology is already present when an individual presents with cognitive symptomology. Patients with MCI exhibit declines in memory and thinking abilities but have preserved activities of daily living. Approximately 32% to 38% of individuals diagnosed with MCI develop AD in 5 years (Mitchell & Shiri-Feshki, 2009; Ward, Tardiff, Dye, & Arrighi, 2013). In other words, not all individuals with MCI develop AD. Identifying risk factors and/or protective factors associated with progression from MCI to AD is crucial.

As mentioned previously, we lack a complete understanding of AD progression. However, there is extensive literature on risk factors and protective factors for AD including genetics, age, social engagement, education, and physical activity (Lindsay et al., 2002; Saczynski et al., 2006). Another important, and modifiable, factor is diet; certain dietary components can be protective while others can be risk factors. In this thesis, the aim is to determine whether aspects of diet implicated in the development of AD are also associated with MCI. Better understanding dietary differences between individuals with MCI and AD could provide insight into why some individuals with MCI progress to AD and other do not.

Alzheimer's Dementia and Mild Cognitive Impairment

Alois Alzheimer reported the first case of AD in 1906. His case study examined a woman who developed memory impairment and other impairments in cognitive functioning, which progressively worsened until her death. What begins with loss of

recent memory and forgetfulness, then progressively gives way to confusion, restlessness, agitation, judgement errors, and reduced capacity to learn. Autopsy revealed widespread neocortical atrophy to which the memory impairments were attributed (Squire et al. 2013). The original case study of AD consequently provided an accurate description of the clinical course most patients follow. Mild cognitive impairment (MCI), as mentioned previously can be a significant risk factor for AD and most researchers and clinicians believe MCI falls on the mild end of the spectrum of AD when Alzheimer's pathology is present. While both MCI and AD involve cognitive decline, the key difference is that patients with MCI have preserved activities of daily living. In other words, their disease has not yet impaired them functionally.

Additionally, an important distinction in terminology regarding Alzheimer's disease and Alzheimer's dementia should be noted. Under recent guidelines from the National Institute on Aging and the Alzheimer's Association, Alzheimer's disease is a diagnosis that can be given to anyone presenting with the pathological hallmarks of Alzheimer's: those with dementia due to Alzheimer's pathology, those with MCI due to Alzheimer's pathology, and even those whose brain changes precede cognitive decline (McKhann et al, 2011). Consequently, what is henceforth referred to in this paper as AD is "dementia due to Alzheimer's disease" or "Alzheimer's dementia." The MCI group referred to in this paper were recruited because of their clinical diagnosis of MCI due to suspected AD.

Cognitive diagnosis. AD is diagnosed in much the same manner as MCI in that the first step to diagnosis is administration of a battery of cognitive testing in a clinical setting. Exact assessments used may differ between physicians; however, the

neuropsychological tests aim to assess a broad array of cognitive functioning. Such tests may include the Mini Mental Status Exam (MMSE) to assess global cognitive functioning, the Boston Naming Test to assess language and naming, the Rey-Osterrieth Complex Figure test to assess visuospatial ability, and/or the Hopkins Verbal Learning Test to assess verbal memory. Clinicians use informed, professional judgement in determining whether dementia is present. MCI can be classified as either amnestic or nonamnestic. Amnestic MCI is characterized by clinically significant declines in memory that do not meet criteria for dementia. Patients with amnestic MCI are increasingly forgetful but have relatively preserved executive functioning, visuospatial skills, and language skills (Petersen, 2011). Nonamnestic MCI is characterized by subtle declines in non-memory domains of cognition, such as those affecting attention, use of language, and visuospatial skills. Nonamnestic MCI is likely a precursor to other forms of dementia other than AD (Petersen, 2011). Patients with dementia, such as AD, will have poorer cognitive functioning (score poorer on the cognitive battery) than those with MCI with their deficits being more pronounced. Difficulty forming new memories and decreased episodic memory becomes more pronounced and is later followed by disorientation to place and time, confusion, impaired communication, behavioral changes, impaired reasoning, and—eventually—difficulty speaking swallowing and walking (McKhann et al., 2011). Additionally, demented patients must have functional impairments or impaired daily living activities for a clinician to consider them to have progressed from MCI to AD or another dementia. The degree of cognitive impairment at the time of diagnosis is a significant predictor of progression, likely because patients with greater impairment at baseline are already closer to the threshold of dementia (Petersen, 2011).

Neural substrates. Alzheimer's changes the whole brain, which explains why the cognitive symptoms are not only evident in multiple domains of cognition, but disease progression is also different from patient to patient. By late-stage AD, the distribution of pathology is extensive. In the case of MCI due to Alzheimer's disease (as assessed in this study), the brain areas affected in MCI are believed to be the same as those affected by AD but to a lesser degree. MCI autopsies are uncommon because most patients progress to Alzheimer's dementia before death but they do reveal an intermediate stage between normal cognition and dementia (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). Other small-scale studies show that MCI patients demonstrate neurofibrillary pathologies in the medial temporal lobe and propose that these contribute to memory impairment (Petersen, et al., 2001). The progressive accumulation of amyloid plaques, tangles, and other neuropathological lesions is believed to underlie the clinical progression of MCI to AD.

Hippocampus. The hippocampus plays a critical role in learning, emotion, and memory. Hippocampal lesions or damage to the hippocampus significantly impairs an individuals' ability to form new memories. The hippocampus is the first clinically significant brain area affected by AD; therefore, over the course of the disease, it becomes the most damaged. This also explains why memory impairment is the first symptom of AD and why memory progressively declines. AD often most detrimentally effects the hippocampus via neuronal degradation or nerve cell loss. Neuronal loss is seen in the hilus and subiculum of the hippocampus in normal aging and in AD but AD patients also exhibit neuronal loss in the CA1 region of the hippocampus and this loss is greater than any other neuronal loss in hippocampal subdivisions (West, Coleman, Flood, & Troncoso, 1994). This evidence suggests that the mechanisms behind Alzheimer's

related neuronal loss differ from the mechanisms of normal aging neuronal loss. Neuronal loss can in part be explained by the lack of hippocampal neurogenesis. Emerging evidence has indicated that altered neurogenesis in the adult hippocampus represents an early critical event in the course of AD. Although causal links have not been established, a variety of key molecules involved in AD pathogenesis have been shown to impact new neuron generation, either positively or negatively (Mu & Gage, 2011). Neuronal loss may also be a result of chronic inflammatory processes. In addition to neuronal loss in the hippocampus, the hippocampus also appears to have reduced functional connectivity in patients with AD. AD patients have decreased functional connectivity of the hippocampus throughout the cerebral cortex, limbic areas, subcortical regions, and cerebellum (Allen et al., 2007).

Atrophy. AD patients generally present with symmetric overall brain atrophy. Atrophy can best be seen on MRI with visually the distance between skull and brain tissue, dilated ventricles, and increased sulci diameter. Essentially, the brain shrinks as a result of widespread cell death resulting from inflammatory processes. They tend to have widespread cortical gray matter loss with greatest grey matter deficits in the temporo-parietal cortices, with sensorimotor and occipital cortices spared comparatively. Grey matter loss is also greater in the left hemisphere (Thompson et al, 2001). Additionally, atrophy/cell death spreads in a predictable pattern that begins in the hippocampus, then deteriorates the cerebral cortex and association cortices, and finally, in later end stages, damages motor cortices.

Featured Neuropathology. Neuropathological diagnostic hallmarks of AD are amyloid plaques and neurofibrillary tangles. Amyloid plaques and neurofibrillary tangles

were historically only confirmed at autopsy; however, new PET scanning and cerebrospinal fluid markers can reliably detect amyloid and tau pathology (Small et al., 2006; Tapiola et al., 2009). However, amyloid and tau have been challenged as disease hallmarks. Plaques and tangles are found in some brains of cognitive healthy elderly individuals. Rezvanian (2016) and colleagues examined the brains of eight individuals aged 90 and over who performed extremely well on memory tests. Neurohistochemical analysis revealed a broad range of AD pathology in the brain. Notably three of the eight brains examined met full criterion for AD despite lack of memory impairment. Additionally, in those with full disease pathology, neurons in the hippocampus were relatively intact. These findings suggest mechanisms may at place in certain individuals protecting them against the effects of AD's pathology. One possible protective mechanism preventing individuals with AD pathology from progressing from MCI to AD could be their diet. As we will argue is this paper, pro- and anti-inflammatory components in an individual's diet, as measured by the dietary inflammatory index, can create individualistic differences in chronic inflammation that may influence AD progression.

Amyloid plaques. Amyloid plaques are composed of β-amyloid proteins—fragments of the larger amyloid precursor protein—that have inefficiently been recycled and thus stick together forming plaques. In a healthy brain, β-amyloid fragments would be broken down and eliminated. However, in an AD brain, β-amyloid fragments resulting from atypical cleavage of the amyloid precursor protein form small clumps of oligomers, then chains of such clumps called fibrils, then fibrils aggregate to form beta-sheets, and, finally, beta-sheets clump to form plaques (Hardy & Allsop, 1991). Recent studies found

that AD-related amyloid oligomers—independent of amyloid plaques—appear to be toxic themselves more so than the plaques. Accumulation of β-amyloid oligomers depresses synaptic excitatory transmission, triggers abnormal patterns of neuronal activity, and contributes to destabilization of neuronal networks (Palop & Mucke, 2010). Additional hypotheses as to why amyloid accumulation causes toxicity include that it may stimulate calcium influx, which induces cell death or that amyloid plaques stimulate the formation of free radicals that induce cell death. However, amyloid also provides normal functions in the brain such as response to a variety of environmental stressors and induction of pro-inflammatory processes. In addition, amyloid may be an antimicrobial peptide that acts as part of the brain's immune system. How these normal functions may or may not relate to amyloid dysfunction in Alzheimer's pathology is unknown (Gkosh, Agarwal, & Haggerty, 2011). Additionally, the hippocampus is believed to be most susceptible to β-amyloid pathology and once the process of plaque formation begins there, it then spreads to other brain areas like the association cortices mentioned earlier.

Neurofibrillary tau tangles. Tau is a protein associated with microtubules in neuronal axons that regulate microtubule growth, assembly, and cross-linking. Hyperphosphorylation of tau resulting in neurofibrillary tangles is also believed to be an important factor AD. In a degraded neuron, tau is found throughout the neuron—not just in the axons—and tau is also hyperphosphorylated. Because tau distribution varies in AD from normal aging, it has been asserted once again that Alzheimer's disease is not just accelerated aging (Waymire, 2017). Neurofibrillary tangles present in AD are stereotypically seen in layer II neurons of the entorhinal cortex, the CA1 and subicular

regions of the hippocampus, the amygdala, and the deeper layers (layers III, V, and superficial VI) of the neocortex (Perl, 2010).

Granulovacuolar degeneration. Granulovacuolar degeneration is not only another hallmark feature of AD, but it has also been observed in other dementias. Granulovacuolar degeneration is characterized by accumulation of large membrane-bound vacuoles in the neurons of multiple brain regions, but especially the hippocampal pyramidal neurons (Funk, Mrak, & Kuret, 2011). Granulovacuolar degeneration often appear in relation to hippocampal phosphorylated tau accumulation (Yamazaki et al., 2011). Additionally, increased accumulation of granulovacuolar degeneration bodies increases as cognition and memory decreases.

Amyloid angiopathy. Another major contributor to AD pathogenesis is cerebral amyloid angiopathy. Amyloid deposition in and around cerebral blood vessels generates response mechanisms including but not limited to changes in blood-brain barrier integrity, edema formation, and the release of inflammatory mediators (Ghiso et al., 2010). Additionally, amyloid build-up around blood vessels chronically limits blood supply which triggers secondary metabolic reactions such as the formation of free radicals that consequently cause oxidative stress and neuronal toxicity (Ghiso et al., 2010).

Acetylcholine hypothesis. While other neurotransmitters like norepinephrine, serotonin, and somatostatin show degradation in AD, acetylcholine has received the most attention because the acetylcholine system appears to be impacted most by AD, especially choline acetyltransferase. Acetylcholine is an important neurotransmitter in memory and it is decreased in individuals with AD. Evidence shows that AD patients

have deterioration of the cholinergic system connecting the midbrain nucleus basalis to the cerebral cortex. Logically, cholinesterase inhibitors are the main drug available to treat AD. These include Donepezil (Aricept) and Rivastigmine (Exelon). Because studies examining medications that enhanced the body's acetylcholine production yielded no effect, we now use cholinesterase inhibitors to inhibit the breakdown of acetylcholine thus increasing the neurotransmitter's bioavailability (Dash & Villemarette-Pittman, 2005).

Neuroinflammation. Neuroinflammation is believed to be another hallmark feature of AD. β-amyloid fragments, mentioned previously, invoke an immune response from microglia causing the release of inflammatory mediators which subsequently contribute to disease progression and severity (Heneka et al, 2015). β-amyloid has also been shown to act as a pro-inflammatory agent itself causing the activation of other inflammatory components and the complement system (Tuppo & Arias, 2005). Additional evidence for the role of inflammation in AD has come from studies that demonstrate that individuals taking anti-inflammatory drugs had lowered risk of developing AD (Tuppo & Arias, 2015). Growing evidence suggests that oxidative stress is also a key factor in the development and progression of AD and MCI (Zhao & Zhao, 2013). The exact mechanism causing disruption of redox balance and the source of free radicals is unknown, but the resulting oxidative stress has been implicated in β-amyloid and tau toxicity, forming a viscous cycle (Zhao & Zhao, 2013). Numerous inflammatory compounds have been implicated in the development and progression of AD and there is no one single compound responsible. Neuroinflammation in AD and MCI is complex and undoubtedly involves synergistic interactions.

Influences of Diet on Dementia

One such way researchers have proposed to lower inflammatory burden in patients with MCI and AD is by diet management. The Mediterranean Diet is a heart-healthy and healthy-aging diet and has been associated with reduced cardiovascular disease, reduced risk of cancer, and reduced risk of AD (Martinez-Gonzalez et al 2015; Lorgeril et al, 1998; Gu, Luchsinger, Yaakov, & Nikolaos, 2010). Additionally, the Mediterranean Diet has been associated with lower risk of prevalent AD, incident AD, incident MCI, and MCI conversion to AD (Gu, Luchsinger, Stern, & Scarmeas, 2010). Key components of the diet are anti-inflammatory foods that include substitution of olive oil for butter and other oils, drinking red wine in moderation, using spices and herbs rather salt, limiting red meat consumption and increasing fish consumption, and eating primarily plant-based foods such as legumes, nuts, fruits, and vegetables. Part of the efficacy of the Mediterranean Diet comes from its promotion of a number of dietary factors rather than from promotion of a single dietary component. Some studies suggest that increased consumption of vitamins C, E, B6, and B12, and folate, unsaturated fatty acids, and fish are related to a low risk of AD, but reports are inconsistent (Luchsinger & Mayeux, 2004). Additionally, randomized clinical trials of supplements of vitamins E, B12, B6, and folate have shown no cognitive benefit (Luchsinger, Noble, & Scarmeas, 2007). The existing evidence does not support the recommendation of specific supplements or dietary components for the prevention of AD or slowed progression of MCI to AD.

Omega-3 Fatty Acids

While evidence from specific dietary components is often inconclusive, omega-3 fatty acids have been consistently shown to be neuroprotective. Polyunsaturated fatty acids influence inflammatory cell function and thereby inflammatory processes. Increased omega-3 fatty acid intake has been shown to lower risk of AD (Boudrault, Bazinet, & Ma, 2009). In a double-blind, placebo-controlled study, monotherapy with omega-3 fatty acids was shown to improve cognition in patients with MCI compared to controls, yet this effect was not seen in patients with AD (Chiu et al, 2008). However, new evidence suggests that efficacy of therapeutic doses of omega-3 fatty acids depend on dietary omega-6 fatty acid consumption. Western diets are deficient in omega-3 fatty acids yet have excessive amounts of omega-6 fatty acids. According to Simopoulos (2002), increased dietary omega-6 polyunsaturated fatty acids (in addition to high omega-6/omega-3 ratio) promotes the pathogenesis of cardiovascular disease, cancer, and inflammatory and autoimmune diseases. However, increased dietary omega-3 fatty acid (low omega-6/omega-3 ratio) exerts suppressive effects. The ratio of omega-6 to omega-3 may be more valuable in analyzing diet than analyzing omega-3 consumption alone. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. Lower omega-6/omega-3 fatty acid ratios are most desirable.

Dietary Inflammatory Index

As evidence linking one specific dietary parameter conclusively to AD and MCI does not exist, it is beneficial to examine diet as a whole. For example, pro-inflammatory diets can lead to chronic inflammation which is implicated in a number of diseases. Shivappa, Steck, Hurley, Hussey, and Hebert (2014) developed the Dietary Inflammatory

Index (DII) to compare populations on the inflammatory potential of their diets. They reviewed the effect of 45 food parameters on inflammatory markers. Based on literature review, food parameters were scored between -1 (meaning the parameter was highly anti-inflammatory) and +1 meaning the parameter was highly pro-inflammatory). The DII used a robust literature base (approximately 6500 articles published up until December 2010) and allows for standardization of individual diets to global referent values. The DII is a unique tool for analyzing intakes on inflammation-modulating foods.

Method

Data used for this current study came from participants in two previous studies. Participants with AD and healthy controls were part of a broader study on the interaction effects between stress and diet on the development of AD. Patients with AD were recruited from the University of Missouri-Columbia neurology clinic. Participants were eligible if they had a clinical diagnosis of dementia due to AD, a clinical dementia rating (CDR) of 1 meaning that they fully progressed to dementia, and no other neurodegenerative diagnoses unrelated to AD. Participants with AD also needed to have a Mini Mental Status Exam (MMSE) score of 23 or less. The MMSE is a cognitive task designed to assess global functioning across several cognitive domains including memory with scores ranging from 0 to 30. Healthy controls were recruited via flyers, web list-serves, and email. Controls were excluded from participation if they had a history of neurodegenerative diagnoses. Participants in the AD group and control group were excluded if they had a known bleeding disorder, or any confounding neurological disorders that effect cognition. Participants with MCI were part of a broader clinical trial examining the effects of elderberry juice on cognition and inflammation in patients with MCI. We recruited patients with MCI from the neurology clinic at the University of Missouri-Columbia. Participants are included in study enrollment if they have a clinical diagnosis of MCI due to AD with a CDR score of 0.5 and a MMSE score of at least 24. The CDR of 0.5 indicates that they exhibit declines associated with dementia but have not progressed to a state of dementia. Participants could not have a current diagnosis of diabetes, a bleeding disorder, or were currently pregnant. Participants also could not have any condition the neurologist believed would impair their ability to complete study

procedures (e.g. terminal illness, comorbid major psychiatric disorders such as schizophrenia, or drug abuse) or any potentially confounding neurodegenerative diseases (e.g. multiple sclerosis). All participants were required to be at least 50 years of age or older. Additionally, all participants completed a standardized Mini Mental Status Exam (MMSE).

Food Frequency Questionnaire

All participants completed a food frequency questionnaire (FFQ) designed by Ritter-Gooder, Lewis, Heidal, and Eskridge (2006) to assess dietary omega-3 fatty acid intake over the past month. Food items assessed via the FFQ were divided into the following groups: Seafood and fish, meat, eggs, dairy products, vegetables, fruits and fruit juices, nuts/seeds, breads/cereals/grains, fats and oils, legumes and products, and herbs and spices. For each food item, participants were asked to note both their usual serving size and how often they usually ate the food item. Serving size options were small, medium, and large. A medium serving size was equal to the serving listed on the form (3 ounces for seafood and fish, ½ cup for vegetables, 1 ounce for nuts, etc.). A small serving size was equal to about half of the medium serving and a large serving size was equal to about one and half as much of the medium serving or more. In our assessment of the FFQs, a small portion size was scored as 0.5, a medium portion size was scored as 1, and a large portion size was scored as 1.5. Options for how often participants consumed the foods included once a month, less than once a week, 1-2 times a week, 3-4 times a week, 5-6 times a week, daily, and more than once daily. In our assessment of the FFQs, once a month was scored as 1, less than once a week was scored as 3, 1-2 times a week was scored as 6, 3-4 times a week was scored as 14, 5-6 times a week was scored as 22,

daily was scored as 30, and more than once daily was scored as 60. Portion size was multiplied by the amount of omega-3 fatty acid (or omega-6/omega3 ratio) in a medium serving as obtained by the USDA Food Composition Database to obtain a measurement of how much of the food component the person consumed in a serving. Next, that number was multiplied by the frequency of consumption over the past month to obtain an estimate of how much of the food parameter was consumed over the past month.

Dietary Inflammatory Index

Using the USDA Food Composition Databases, we determined how much of each of the food parameters included in the DII effect scores were in each food assessed by the FFQ. First, we assessed how much of each food parameter was consumed by participants on a monthly basis. In order to do this, we multiplied the amount of the food parameter in a medium serving of a food item by the self-reported portion size consumed by the participant and then multiplied that by the self-reported frequency of consumption over the past month. Then, we repeated this process for each food item assessed and added them together to achieve an estimated total monthly consumption of each food parameter by each participant. For example, in assessing the omega-3 fatty acid intake of an individual, we would start with the amount of omega-3 fatty acid in a medium serving of each food item. For example, for tuna, the USDA reports there to be 0.230 grams of omega-3 fatty acid in a 3 ounce serving of tuna. If a participant reports eating a small serving (0.5) of tuna daily (30), we would estimate that he is consuming 3.45 grams (0.23*0.5*30) of omega-3 fatty acid from tuna on a monthly basis. This process is repeated for all food items and added. Next, we assessed the total DII for each participant based on the available dietary data assessed in the FFQ. Following the methodology

developed by Shivappa, Steck, Hurley, Hussey, and Hebert (2015), we calculated z-scores and centered percentiles for each of the food parameters for each individual participant based on the global mean daily intake and standard deviation provided by Shivappa et al. (2015). Next, the centered percentiles for each food parameter was multiplied by the overall food parameter-specific inflammatory effect score to obtain the food parameter-specific DII score. Summation of the food parameter-specific DII scores created the overall DII scores for an individual.

Results

We recruited 56 total participants (17 with AD, 19 with MCI, and 20 healthy controls). Groups did not differ significantly by age or gender. Mean ages for AD, MCI, and healthy control groups were, respectively, 78.6, 76, and 66.2 years. AD, MCI, and healthy control groups were 56%, 58%, and 60% female, respectively. Approximately half (n=9) of the participants with AD were unable to complete the MMSE due to their being in the later stages of the disease course. Scores on the MMSE averaged 18 for the remainder of the AD group, 24 for the MCI group, and 29 for healthy controls. Using one-way ANOVAs, we aimed to understand whether or not participant type had a significant effect on the specific food parameters and/or DII; in other words, do the food parameters and/or DII explain a significant portion of the variance between controls, MCI group, and AD group.

Omega-3 Fatty Acids

One-way ANOVA revealed that there was a significant effect of participant type on omega-3 fatty acid consumption, $F(2,53) = 3.59$, $p = 0.04$. Post hoc comparisons using Tukey's B test indicated that the mean omega-3 fatty acid consumption for controls ($M = 42.41$, $SD = 27.35$) significantly differs from the AD group ($M = 16.17$, $SD = 8.63$). However, neither the controls nor AD group significantly differed from the MCI group ($M = 33.71$, $SD = 42.37$).

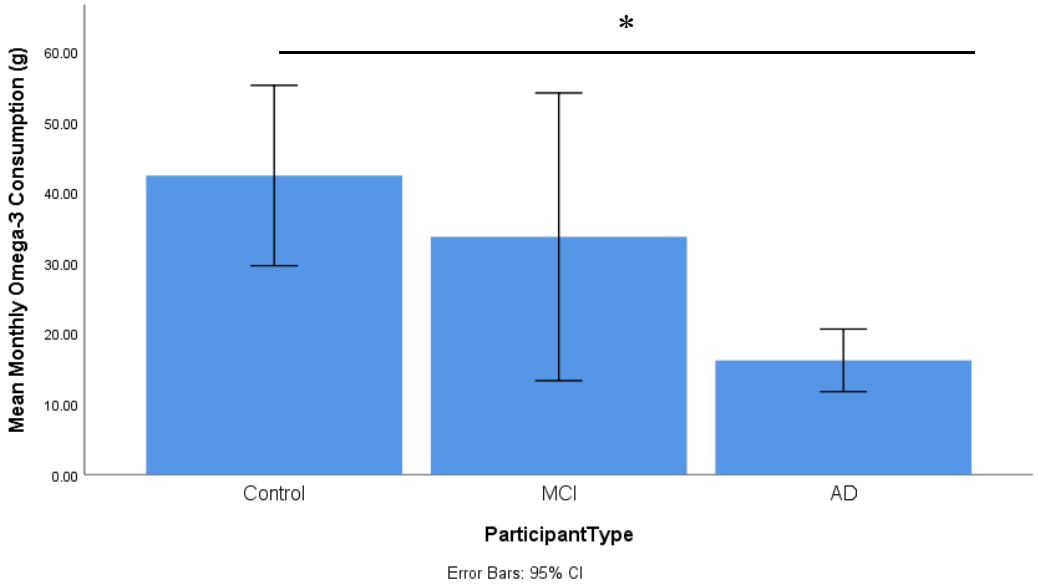

Figure 1. Mean monthly omega-3 fatty acid consumption (g) for controls, MCI group, and AD group. *p<0.05

Omega-6/Omega-3 Fatty Acids Ratio. One-way ANOVA revealed that there was no significant effect of participant type on omega-6/omega-3 fatty acids ratio, $F(2,53) = 0.68$, $p = 0.51$.

Dietary Inflammatory Index

One-way ANOVA revealed that there was a significant effect of participant type on DII, $F(2,53) = 8.54$, $p = 0.001$. Post hoc comparisons using Tukey's B test indicated that the mean DII for controls ($M = -3.16$, $SD = 1.17$) was significantly different from both the MCI group ($M = -2.02$, $SD = 1.40$) and AD group ($M = -1.67$, $SD = 0.77$). However, the MCI and AD groups did not significantly differ.

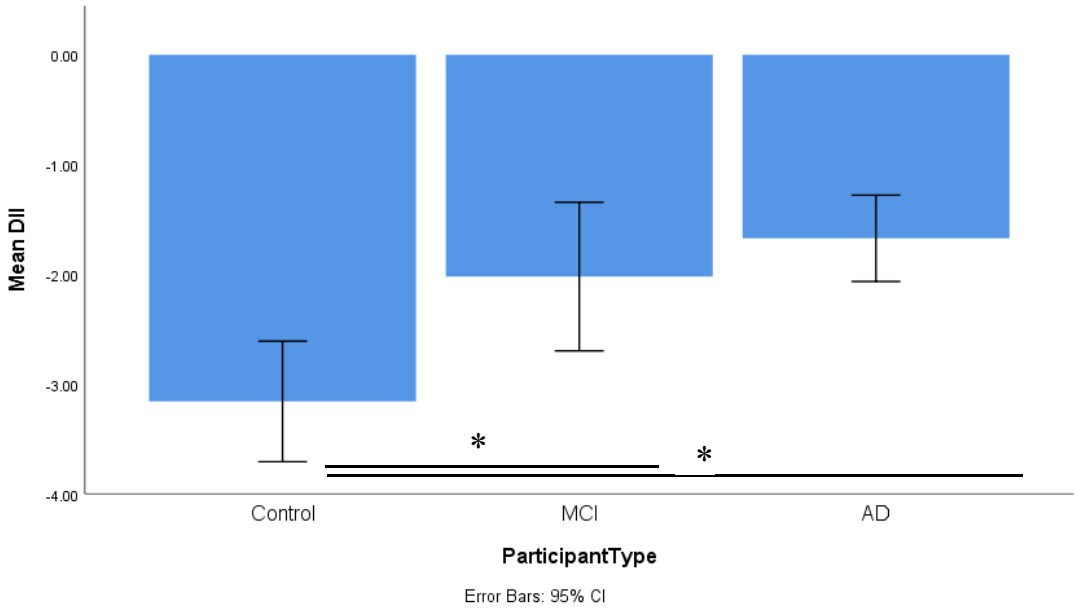

Figure 2. Mean dietary inflammatory index for controls, MCI group, and AD group. *p<0.05

Discussion

As expected, we found that omega-3 fatty acid intake significantly differed between healthy controls and patients with AD; omega-3 fatty acids have been well-established as neuroprotective. However, there was no difference in omega-3 fatty acid intake between the MCI group and controls or the AD group. This may be due to the large standard deviation of omega-3 fatty acid intake in the MCI group. This also may be due to our small sample size. We found no significant differences in omega-6/omega-3 fatty acid ratio between controls, the MCI group, and the AD group. This is likely due the fact that our FFQ was designed to measure foods high in omega-3 and not omega-6.

We found that dietary inflammatory index significantly differs between controls, patients with MCI, and patients with AD; controls have the most anti-inflammatory diet and patients with AD having the least anti-inflammatory diet. This evidence could support the role of inflammation in the development and progression of AD and the influence of inflammatory diet on disease progression. However, it is important to note a few other factors that may influence differences in dietary inflammation. First, as diet is more modifiable than other factors influencing AD, patients can change their diet as a protective measure against disease onset or progression. As patients notice cognitive decline or are diagnosed with MCI and/or AD they may implement a more anti-inflammatory diet or the Mediterranean diet. If this were an explanation of our results, however, we would have seen that individuals with MCI and AD had more anti-inflammatory diets than controls and we in fact saw that controls had the most anti-inflammatory diet. Second, and more probably, behavioral dysregulation as AD progresses could result in worsening of diet. Memory decline associated with dementia

can affect eating habits in that a person may forget meals and skip them altogether or eat multiple meals as they forgot they had recently eaten. As AD progresses, chewing and swallowing can become more difficult which limits the foods an individual can eat. As such, it is uncertain whether differences in diet are due to disease progression or vice versa.

Limitations

Our analysis of diet was limited by our measurement of diet. The FFQ used was designed to assess omega-3 fatty acid intake. However, as mentioned previously, this FFQ did not assess consumption of many omega-6 rich foods like processed foods or sweets. Additionally, foods high in omega-3 fatty acid are generally anti-inflammatory (having a DII of closer to -1) and foods high in omega-6 are generally pro-inflammatory (having a DII of closer to +1). This may also explain why all three of our groups had negative mean DIIs, as our FFQ did not assess many pro-inflammatory foods. Additionally, we were unable to control for variances in calorie intake as our FFQ did not access such common, high-calorie foods as fast food items, dessert, and packaged or processed foods.

Another weakness to the FFQ was that it was a retrospective self-report measure. Healthy controls generally filled out the FFQ for themselves and caregivers filled out the FFQ for individuals with AD. Some participants with MCI filled out the FFQ themselves while others had a caregiver fill it out. The measure's retrospective nature makes it subject to inaccuracy, as such responses on the FFQ were regarded as a rough estimate of food intake over the past month. Also, the FFQs for the AD and control groups were completed approximately 10 years prior to the FFQs for the MCI group which may result

in dietary differences based on dietary trends across time. Participants with memory impairments are not reliable self-reporters.

The study from which the AD and control participant FFQs were taken did not assess participant demographics other than age and gender. Education level and physical activity levels were not assessed in the AD or control groups. Physical activity levels were also not assessed in the MCI group. These factors would have been important to consider as we know that lower education is often associated with greater risk of dementia (Sharp & Gatz, 2011) and physical activity has been associated with lower risks of cognitive impairment, Alzheimer's disease, and dementia of any type (Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K, 2001). Additionally, both studies from which dietary data was taken had small sample sizes that make interpretation of results difficult. A more statistically meaningful component analysis could not be performed due to sample size.

In our examination of omega-3 and omega-6 fatty acids, it would have been beneficial to examine or control for whether participants in any group were taking omega-3 supplements, such as fish oil. Although omega-3 supplementation was not assessed on the FFQ, it could have still been calculated into the DII scores.

Future Directions

Future directions of this work should examine DII using a more comprehensive FFQ, especially adding assessment of common pro-inflammatory foods. Current trends in diets and geographic differences in diet as well as access to certain foods should be considered. Ideally, a food log that is filled out daily would be used as opposed to a

retrospective measure. Development of a smart phone app to log food items daily and automatically calculate DII should be considered. However, it is important to note that individuals with memory impairments (such as those in the MCI and AD groups) may still provide unreliable self-report data.

At this time, it cannot be inferred that there is a causal relationship between inflammatory diet and AD progression. More work is needed to parse out this relationship and the best way to do so is to control for diet. One such way would be to examine an animal model of AD and administer pro- and anti-inflammatory diets to determine if the diet directly influences dementia progression.

Future directions will also involve the study of interactions between diet and other factors in the progression and development of AD. One such factor we plan to study is stress. Wilson et al. (2002; 2007) found that individuals prone to psychological stress had an increased risk in developing MCI and AD. Dietary factors and stress have been reliably been shown to influence the development of AD independently; yet, it is unknown whether they interact.

As our goal was to examine whether modifiable factors influence AD development, these findings can be used to inform individuals at risk for developing AD (for example, individuals with MCI) to maintain an anti-inflammatory diet. Individuals could add foods; especially high anti-inflammatory food components analyzed by the DII to their diet and set dietary goals using the DII to lower chronic inflammation.

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