5-2015

The Role of Diet, Erythrocyte Membrane Fatty Acid Composition, and Alzheimer's-related Genes in Systemic Inflammation in the Cache County Memory Study

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THE ROLE OF DIET, ERYTHROCYTE MEMBRANE FATTY ACID COMPOSITION, AND ALZHEIMER'S- RELATED GENES IN SYSTEMIC INFLAMMATION IN THE CACHE COUNTY MEMORY STUDY

By

Rola Adnan Jalloun

A dissertation submitted in partial fulfilment

Of the requirement for the degree

of

DOCTOR OF PHILOSOPHY

in

Nutrition, and Food Sciences

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UTAH STATE UNIVERSITY

Logan, Utah

2015

ABSTRACT

The Role of Diet, Erythrocyte Fatty Acid Concentration, and Alzheimer's-Related

Genes in Systemic Inflammation

in the Cache County Memory Study

by

Rola A. Jalloun, Doctor of Philosophy

Utah State University, 2015

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This project examined the association between dietary patterns, erythrocyte membrane fatty acids concentration, and Alzheimer's-related genes in systemic inflammation, as indicated by C-reactive protein (CRP) levels, in order to achieve more comprehensive knowledge of how nutrition and genetics influence systemic inflammation among the elderly residents of Cache County, Utah.

First, the associations between dietary patterns defined by Dietary Approaches to Stop Hypertension (DASH) and Mediterranean dietary patterns (MED) and the risk of having a high level of CRP were examined. This study showed that a healthy dietary pattern score was associated with CRP levels; a higher score reflecting the ideal DASH diet and MED diet was associated with a 26% and 27% reduction in the risk of having high CRP levels respectively. This association appeared stronger among overweight and obese individuals.

Second, the association between erythrocyte membrane fatty acids (EMFAs) and elevated serum C-reactive protein (CRP) levels was examined. Those that had high EMFAs composition of palmitoleic acid and nervonic acids, both monounsaturated fatty acids (MUFAs), and dihomo-y-linolenic acid (DGLA),

docosapentaenoic acid (DPA-6), docosahexaenoic acid (DHA), all polyunsaturated fatty acids (PUFAs), had an increased risk of having CRP elevation. In contrast, risk of CRP elevation was reduced in those that have highest levels of saturated fatty acids (SFAs) of margaric acid, stearic acid, and arachidic acid. These associations were generally observed to be stronger among women compared to men.

Lastly, the study examined whether AD-related genes identified in previous genome-wide association studies are associated with elevated levels of inflammatory CRP. Results revealed a strong association between APOE-epsilon genotypes and CRP levels. Results also showed an association between major alleles of APOE rs439401, TOMM40 rs157580, and minor alleles MMP8 rs1892886, CR1 rs6656401, CR1 rs3818361, and CR1 rs4844609 that were associated with a risk of elevation of CRP. These associations were stronger among men compared to women.

Reduction in the prevalence of AD could have tremendous importance; the results of this dissertation may help identify factors important to AD etiology and, in turn, provide valuable targets for prevention.

(177 pages)

PUBLIC ABSTRACT

The Role of Diet, Erythrocyte Fatty Acid Concentration, and Alzheimer's-Related

Genes in Systemic Inflammation in the Cache County Memory Study

Rola Jalloun

Alzheimer's disease (AD) is the most common type of dementia in the elderly, accounting for 60 to 80% of all dementia cases. It affects 5.2 million Americans and 44 million worldwide. This project examines the association between dietary patterns, erythrocyte membrane fatty acids concentration, and AD-related genes in systemic inflammation as indicated by serum C-reactive protein (CRP). All studies performed in this project used the data collected in the Cache County Memory Study (CCMS).

Higher levels of accordance with the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean dietary (MED) patterns were associated with consistently lower levels of CRP in elderly men and women. Interestingly, this association appeared stronger among overweight and obese participants when compared with normal weight participants. These results emphasize that the DASH and Mediterranean diets may play an important role in reducing systemic inflammation, which may lower AD risk, especially among overweight and obese persons.

A high erythrocyte fatty acid concentration of palmitoleic acid, and nervonic acids, both monounsaturated fatty acids (MUFAs), dihomo-y-linolenic acid (DGLA), docosapentaenoic acid (DPA-6), docosahexaenoic acid (DHA), all polyunsaturated fatty acids (PUFAs), were similarly associated with increased risk of CRP elevation. Margaric acid, stearic acid, and arachidic acid, all saturated fatty acids (SFAs), were associated with a reduced risk of elevated CRP. These associations was stronger among women than men.

Several AD-related genes were found to influence risk for having CRP elevation. APOE-epsilon alleles were associated with CRP levels among elderly men and women. A major alleles of APOE (C/C) rs439401 and TOMM40 (A/A) rs157580, and minor alleles of MMP8 (T/T) rs1892886, CR1 (A/A) rs6656401, CR1 (A/A) rs3818361, and CR1 (A/A) rs4844609 lowered the risk of elevated CRP among elderly men. These results emphasize the need to consider gene-environment interactions when searching for genes influencing AD risk.

With the increased prevalence of AD and the association of systemic inflammation, the results of this dissertation may help identify factors important to AD etiology and, in turn, provide valuable targets for preventive intervention to improve people's quality of life and nutritional well-being.

ACKNOWLEDGMENTS

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CHAPTER 1

INTRODUCTION

Alzheimer's Disease (AD) is an irreversible, progressive brain disease that slowly degrades the memory and thinking skills and ultimately eliminates the capability to perform the simplest tasks [1]. AD is the most common form of dementia. The Alzheimer's Association documents that Alzheimer's disease (AD) in the U.S. is the sixth leading cause of death for people who are 65 years or older. In 2015, 5.3 million Americans of all ages had AD and 44 million worldwide [2].

Evidence for the role of inflammation in AD still cannot be definitively stated whether inflammation is a cause, contributor, or secondary phenomenon in AD [3]. Biochemical and neuropathological evidence suggest that astrocytes and microglia are the major immune cells in the brain. In AD brain, astrocytes and microglia activate and release inflammatory mediators due to the presence of $A\beta$ plaques and neurofibrillary tangles [4]. Until now, emerging evidence suggests that inflammation in AD is complex, and it involves interaction with multiple factors that challenge the researcher to find ways to tune inflammation to delay, prevent, or treat AD.

Inflammation is the first step of a non-specific immune response that occurs in reaction to any bodily injury [5]. Inflammation can be acute or chronic [5]. When it is acute immediate and rapid response occurs to the site of tissue injury. Chronic inflammation occurs as a result of the progression of the acute inflammation, which may last for weeks or months, and in some instances, for years [6]. In the central nervous system, inflammatory components are linked to AD neuroinflammation. The production of a proinflammatory cytokines such as tumor necrosis factor α (TNF-α) plays a role in brain communication [7]. During infection, extensive communication between the immune system and the central nervous system, in which neural activity

is altered quite extensively during a peripheral infection [8]. Chronic systemic inflammation, as indicated by increases in inflammatory biomarkers were linked with an increase in cognitive decline in Alzheimer disease patients [7, 9-12].

C-reactive protein (CRP) is the sensitive marker of acute-phase response to most forms of inflammation, infection, and tissue damage. Many cytokine levels including interleukin-1β (IL-1β), interluken-6 (IL-6), and tumor necrosis α (TNF-α) enhances CRP expression in humans [13]. It has been proposed that CRP predicts the incidence of many diseases including cancer [14], type 2 diabetes [15], coronary artery disease, heart attack [16], inflammatory bowel disease [17], arthritis [18], pelvic inflammatory disease [19], lupus [18], and AD [20].

Scientific knowledge is far from complete regarding the relationship between peripheral blood inflammatory biomarkers and AD. However, scientific advances recently have been noticeably changing the understanding of the role of high levels of peripheral blood inflammatory biomarkers in AD patients [21]. Strong evidence suggest that CRP levels represented a strong risk predictor of systemic inflammation in 60 patients with Late Onset Alzheimer's Disease (LOAD), 35 patients with (Vascular Disease) VD, 25 subjects affected by cognitive impairment no-dementia (CIND), and 40 cognitively normal controls [22]. O'Bryant et al. observed the same when he evaluated CRP levels and compared 192 patients with AD with 174 non-demented [23].

Diet may influence the risk of AD and through its effects on systemic inflammation [24]. Dietary components are important factors that should be considered in inflammatory processes [25]. The Dietary Approaches to Stop Hypertension Diet (DASH) and the Mediterranean diet (MED) have been associated with protection against cognitive decline [26] and reduced risk for inflammatory

biomarkers and AD [27, 28]. In recent years, a rapidly increasing number of studies reported that due to the components of both diets components, the DASH and Mediterranean diets are considered to be anti-inflammatory [29, 30]. These findings support the hypothesis that DASH diet and the Mediterranean diet may be associated with inflammatory biomarkers level in several conditions such as myocardial infarction [31], diabetes [32], elevated triglycerides, elevated systolic and diastolic blood pressure, colorectal cancer, insulin resistance, HDL cholesterol [33, 34], and AD [27].

The metabolic effects of some diets may be attributable to pro-inflammatory and anti-inflammatory properties [35] and their dietary constituents including aspects of the Western diet such as higher intake of the fats and processed meats [36]. Fatty acid is a carboxylic acid with a long aliphatic tail (chain), which is either saturated or unsaturated [37]. The two main essential fatty acids are linoleic acid (LA) omega-6 fatty acid, and α-linolenic acid (ALA) omega-3 fatty acid [38]. Both omega-6 and omega-3 polyunsaturated fatty acids (PUFA) play important roles in the regulation of inflammation by being precursors of potent lipid mediators [39] and altering gene expression [40]. High intake of fatty fish or n-3 PUFA oil fish supplements may improve anti-inflammatory profiles by changing the production of lipid mediators and regulating immune responses [39]. Consuming refined vegetable oils rich in omega-6 fatty acids and foods containing a low level of long-chain omega-3 fatty acids has been associated with an increase in inflammation levels [41] in some but not all studies.

Genes associated with AD may influence AD risk via their effects on inflammation. It has been proposed that the overall chances of an individual developing AD is strongly influenced by a "susceptibility profile" reflecting the joint

effects of inheriting multiple high-risk alleles and environmental factors. In complex inflammatory diseases, inflammation gene polymorphisms may alter gene expression and function [42]. Gene polymorphisms in both acute and chronic inflammation produce different types of inflammatory responses [43]. The risk of AD was substantially affected by ten polymorphisms in many inflammatory biomarkers [44, 45].

Dissertation Hypotheses and Objectives

The purpose of this study is to determine the extent to which dietary factors, erythrocyte membrane fatty acid, and genes, previously associated with C-reactive protein (CRP) markers of systemic inflammation among participants in the Cache County Memory Study. The specific objectives and hypotheses of this dissertation are:

1. To determine whether healthy dietary patterns, defined by the DASH and Mediterranean diets, are associated with a reduced level of systemic inflammation as indicated by level of inflammatory CRP in plasma obtained from participants in the Cache County Memory Study (CCMS).

2. To determine whether erythrocyte membrane fatty acids are associated with elevated levels of inflammatory CRP in the Cache County Memory Study (CCMS).

3. To determine whether AD-related genes, identified in previous genome-wide association studies, are associated with elevated levels of inflammatory CRP in the Cache County Memory Study (CCMS).

Dissertation Structure

This dissertation is divided into six chapters. Chapter 1 provides an introduction to the research along with outlines covering study objectives and hypotheses. Chapter 2 is titled "The role of diet, erythrocyte membrane fatty acid, and Alzheimer's-related genes in systemic inflammation in the Cache County Memory Study: A Review." This chapter provides the literature review of each of these three modifiers and evidence that they are related to the risk of systemic inflammation. Chapter 3 is titled "The role of dietary approach to stop hypertension and Mediterranean-style dietary patterns in systemic inflammation in the Cache County Memory Study." This chapter examines the association between the dietary approach to stop hypertension and Mediterranean- style dietary patterns and CRP levels in the CCMS. Chapter 4 is titled "Erythrocyte membrane fatty acid concentration and systemic inflammation in the Cache County Memory Study." This chapter examines the association between the erythrocyte membrane fatty acid composition and CRP levels in the CCMS. Chapter 5 is titled "The role of Alzheimer's-related genes in systemic inflammation in the Cache County Memory Study." This chapter examines the association between Alzheimer's-related genes and CRP levels in the CCMS. Chapter 6 wraps up with a discussion of the findings and provides conclusions and recommendation for further research directions and practitioners. The references for each chapter were listed at the end of each.

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CHAPTER 2

THE ROLE OF DIET, ERYTHROCYTE MEMBRANE FATTY ACID

CONCENTRATION, AND ALZHEIMER'S- RELATED GENES IN SYSTEMIC

INFLAMMATION IN THE CACHE COUNTY MEMORY STUDY: A REVIEW

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is an irreversible, progressive brain disease that slowly degrades memory and thinking skills and ultimately destabilizes the capability to perform the simplest tasks [1]. It is the most common type of dementia and gradually worsens over time. It accounts for an estimated 60 to 80 percent of all dementia cases. It affects memory, thinking, and behavior. Most often, AD is diagnosed in people over 65 years of age, but the less-prevalent, early-onset of Alzheimer's can occur at a much earlier age. In 2015, Alzheimer's disease affected 5.3 million Americans and 44 million people worldwide. Alzheimer's prevalence is 1 in 9 older Americans. The Alzheimer's is predicted to affect 1 in 85 people globally by 2050. It accounts for over 226 billion dollars in annual costs in the U.S. alone and this is estimated to rise to 1.1 trillion by 2050 [2]. The National Center for Health Statistics 2015 indicates that Alzheimer's disease is the United States' sixth-leading cause of death for people who are 65 years or older [2]. The Alzheimer's Association reported that between 2000 and 2025, the number of people with AD in Alaska, Colorado, Idaho, Nevada, Utah, and Wyoming is expected to double or more. In 2015, the Utah percentage of AD will increase from 45% to 127% by the year 2025 [2]. AD patients need help with daily activities such as bathing, dressing, using the bathroom, and eating [1, 3]. Patients lose their ability to communicate with others; they find it hard to recognize their loved ones, and they spend most of their time in bed with constant caregiver supervision.

The main features of AD include: memory loss, impaired judgment, disorientation, confusion, behavioral changes, and difficulty speaking, swallowing and walking [4]. The main early characteristics of Alzheimer's disease are the loss of neurons and synapses in the hippocampus. These losses caused significant atrophy in some affected areas [5, 6]. In 2009, Clifford and his colleague used magnetic resonance imaging (MRI) to study 21 healthy cognitively normal subjects, 32 with amnestic mild cognitive impairment, and 8 with Alzheimer's disease. In this study, they found that the brain size in AD patients became smaller over the time starting from the mild cognitive impairment stage and worsening until it developed into Alzheimer's disease [7].

There are two types of AD: early onset and late onset [8]. The symptoms for early onset AD appear before age 60. Research has narrowed down the main genetic causes for some early onset as mutations in the amyloid precursor protein (APP) gene located on chromosome 21 and the presenilin gene (PSEN1& PSEN2) [8]. Having any of these mutated early onset AD genes indicates that this person will likely develop AD before the age of 60 and in some cases as early as age 30. This type of AD is called "familial" Alzheimer's disease [9]. Early onset people tend to have shorter survival and these patients show more extensive functional and structural neuroimaging changes than late onset [10, 11]. Late onset Alzheimer's disease (LOAD) is defined by the onset of symptoms after age 65. It has yearly incidence rates rising from 1% at 65–70 years to 6–8% at 85 years and older [12]. Genes play an important role in increasing AD risk, especially for LOAD [13].

Even now it's still hard to identify the main causes of Alzheimer's disease. AD occurs as a result of many diverse risk factors rather than one single factor, and because of that, it is considered a multifactorial chronic disease [14]. Recent data

reports that genetic factors, physical activity, diet, social isolation, cardiovascular disease, and diabetes have been related to AD pathology [15]. For example, a diet high in vegetables, fruit, and fiber intake may lower neurodegenerative disorders risk by affecting the pathological processes of these diseases [16].

Inflammation

The base word for inflammation is the Latin word "inflammare", which means "to ignite or set on fire." Cornelius Celsus, a Roman encyclopaedist, was the first to describe the symptoms of inflammation [17, 18]. Inflammation is a natural step of a non-specific immune response that occurs in reaction to any bodily injury. Inflammation can be acute or chronic [19]. When it is acute, an immediate and rapid response occurs at the site of the injured tissue. The main characteristics of acute inflammation are vascular and leukocyte responses, fluid accumulation, and inflammatory mediators such as cytokines. Acute inflammation has many macroscopic events that lead to rubor (redness), calor (heat), dolor (pain) and tumor (swelling) [18, 20]. The transformation from acute to chronic inflammation is still not completely understood. Excess proinflammatory mediators are a main characteristic of chronic inflammation [21]. Chronic inflammation occurs as a result of inflammatory progression in acute inflammation and may last for weeks or months, and in some instances for years [22]. Chronic inflammation is mainly characterized by tissue destruction and fibrosis combination due to the prolonged and repeated inflammation. Chronic inflammation involves complex interactions between several cell populations and their secreted mediators causing leukocyte activation and excessive infiltration that leads to resultant tissue damage and loss of function [20]. Chronic low-level inflammation is considered to be below the threshold of pain and in

some cases it is called "silent inflammation" [23].

Both acute and chronic systemic inflammations are characterized by increases in inflammatory biomarker levels in blood such as C-reactive protein (CRP), cytokines, and chemokines [24]. In the central nervous system, acute and chronic systemic inflammatory responses may begin with the detection of either bacterial or viral invasions. When the immune response detects bacteria, products are produced that activate diverse innate immune responses such as nucleotide-binding oligomerization-domain protein-like receptors (NLRs) and Toll-like receptors (TLRs) [25-27]. TLRs are a set of single membrane-spanning noncatalytic receptors that recognize structurally conserved molecules derived from microbes. Identification of bacterial products by TLRs and NLRs cause direct cell activation leading to the expression of many immune factors such as proinflammatory CRP, cytokines, and chemokines [28]. Mechanistic studies suggest that viral inflammation has many effects such as damaging the infected cells [29], destroying the body's immune system, altering the genetic material (DNA) of infected cells [30], or causing inflammation that can damage an organ [31].

A large body of epidemiological evidence supports the hypothesis that peripheral inflammatory markers predict disease progression and determine whether therapies targeting these markers alter prognosis in patients with these diseases [32, 33]. Many animal and human studies provide conflicting evidence about whether inflammatory markers are the direct causes of adverse events or if they simply are the result of illness in older adults [34]. When peripheral inflammatory markers were evaluated in elderly patients with Mild cognitive impairment (MCI), AD, and normal elderly, it was found that this method helped to detect early progression of both MCI and AD [35]. Another study concluded the same result when they measured tumor

necrosis factor α (TNF-α) in AD patients [33].

For a long time, the evidence of inflammatory processes in the pathogenesis of AD involvement has been acknowledged, however, the inflammation theory in AD pathology has recently surged to the surface [36]. The fact that diseases with a chronic systemic inflammatory component are risk factors for Alzheimer's disease implies that crosstalk occurs between systemic inflammation and microglia in the Central nervous system (CNS) [37]. Microglial cells are considered the first line of defense in the CNS. In a healthy brain, microglia is relatively inactive, but in AD patients microglia are always switched on [38]. Neuroinflammation is recognized as a downstream consequence of amyloid theories causing activation of microglia and starting a pro-inflammatory cascade. These changes cause neurotoxic substances to release cytokines, chemokines, reactive oxygen and nitrogen species, and various proteolytic enzymes, inducing deteriorating changes in neurons [39]. It has also been proposed that microglia activation may cause phosphorylation of tau and the formation of neurofibrillary tangles (NFTs) [40, 41].

C-reactive protein (CRP)

C-reactive protein (CRP) is a nonspecific marker of an acute-phase response to most forms of inflammation, infection, and tissue damages [42]. Interleukin-1β (IL-1β), interluken-6 (IL-6), and TNF-α are strongly induced by the expression of CRP in human [43] hepatocytes and hepatoma. Human atherosclerotic studies showed that indirect deposit of CRP from circulating cells or direct production of CRP by cells in the arterial wall [44, 45]. Additionally, human neuronal cells were found to produce CRP in Alzheimer's disease patients [46]. CRP has also been found in renal cortical tubular epithelial cells, which can be a result of inflammatory stimuli [47].

CRP has several immune-related functions including: detecting the invading particle to the phagocyte, activation of classical complement binding, modulation of polymorphonuclear function [48], inhibition of growth and/or metastases of tumor cells and a few additional diverse activities [49]. Casas and his colleague reported that the normal function of CRP continues [50]. However, many extensive research projects reported that CRP has a beneficial role in both innate immunities against infection, appropriate, safe handling, and disposal of damaged autologous cells and lipids [50].

Although, in normal healthy subjects CRP is at trace levels in plasma, high levels of CRP indicates that there is inflammation somewhere in the body [51]. The plasma half-life of CRP in humans is about 19 hours which is the same in all individuals regardless of circulating concentrations of CRP [50]. Despite many claims and assertions in the literature, genetic factors may affect the variation in the levels of CRP [52]. Factors including diet and smoking cessation remain critical tools for CRP reduction, and body mass index (BMI) has been associated with inflammatory mediators including CRP [53, 54].

Indeed, CRP is the most extensively studied systemic marker of inflammation [55]. CRP levels have been used to predict the incidence of many diseases including cancer [56], type 2 diabetes [57], coronary artery disease risk, damage from a heart attack [58], inflammatory bowel disease [59], some forms of arthritis [60], pelvic inflammatory disease [61], lupus [60], and AD [62].

Scientific advances have been noticeably changing over the last decades regarding our understanding of the role of high levels of CRP in AD patients. Cross-sectional studies of AD patients and controls found that there were small differences in IL-6, but mean levels of CRP were significantly different between AD cases and

controls [63, 64]. Among 99 cases and 99 controls in a cross-sectional study, the results found high serum CRP levels among demented participants when they were compared with the controls. The same study also compared 34 AD patients with 64 vascular dementia (VaD) patients by checking the CRP levels in both groups. The results indicated that AD patients had higher CRP levels than VaD [65]. An Italian population-based elderly cohort (n = 804, 53.2% women, mean age 74 years old), examined the relationships of baseline plasma CRP, serum IL6, plasma alpha-1-antichymotrypsin, and hyperhomocysteinemia with the risk of incident Alzheimer's disease (AD) and vascular dementia (VaD). The study found that CRP and IL-6 were the only inflammatory biomarkers related to the risk of VaD, but not with the prediction of AD risk [66]. O'Bryant et al., found the same result when they 192 patients with AD and 174 non-demented controls and their CRP levels were evaluated [67].

Diet and Inflammation

Numerous research studies indicate that dietary patterns have been used over the last few decades to analyze human health [68]. While many dietary patterns have been used in human health studies, much evidence shows that Mediterranean Diet [69, 70] and Dietary Approaches to Stop Hypertension (DASH) are effective for a short and long term. Both diets are helpful in fighting or preventing metabolic diseases and are anti-inflammatory [71, 72].

Mediterranean Diet (MED)

The Mediterranean Diet (MED) is a traditional dietary pattern from different countries bordering the Mediterranean Sea. MED is a boasting a modern nutritional recommendation inspired by the time tested way of eating traditional foods and drinks from these countries [73]. The Mediterranean Diet is rich in fruits, vegetables,

legumes, and complex carbohydrates, with a moderate consumption of fish, while the consumption of olive oil is the main source of fat, and with a low-to-moderate amount of red wine during meals [74]. This diet was noted by American scientist Ancel Keys stationed in Pioppi, Italy in 1945, but it didn't gain national attention until the Seven Countries Study reported in 1960 that a Mediterranean Diet is a healthy diet [75].

Many large epidemiologic studies in different cohorts showed that there is a positive association between Mediterranean Diet adherence and a reduction in the risk of mortality and the incidence of major chronic diseases [76, 77]. A systematic review of 12 studies with a grand total of 1,574,299 subjects reported that a high adherence to the Mediterranean Diet in southern Europe is associated with a 6% reduction in cancer, a 9% reduction in total cardiovascular mortality, and a 13% reduction in Parkinson's and Alzheimer's disease incidence [78]. Meta-analysis of a larger number of subjects and studies confirmed that Mediterranean Diet adherence was associated with a lower risk of major chronic degenerative occurrences [79]. Subsequently, these findings were confirmed by Francesco and colleagues, who reported a significant inverse relationship between higher adherences to Mediterranean Diet and a reduced risk of AD [80-82].

Mediterranean diet (MED) and Inflammation

Human observational studies:

Strong evidence suggests that the Mediterranean Diet could serve as an anti-inflammatory diet by reducing CRP concentrations in plasma that have a protective effect against several diseases [83, 84]. Two longitudinal studies reported that a significantly higher adherence to MED reduced CRP levels when a diet score was used to assess MED adherence. The Attica epidemiologic study in Greece examined the high adherence of MED in randomly enrolled 3,042 participants (1,514 men and

1,528 women). They found a higher adherence to MED had on average, 20% lower CRP levels when compared with lower adherence to MED [85]. Later, Panagiotakos et al. found that high adherence to MED had a protective effect that reduces CRP levels by 3.1% after controlling for age, gender, body mass index, physical activity, smoking status, diabetes and medication intake in myocardial infarction (MI) survivors. The study was performed in six European countries: Greece, Germany, Spain, Finland, Italy, and Sweden, which included 200 post-MI survivors [86]. Only one cohort study assessed the association between MED adherence, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. This intervention diet had significantly reduced serum concentrations of hs-CRP, and 118 incident AD cases were identified among the 1,219 non-demented elderly (age $\geq$ 65) after four-year follow up [87]. The Nurses' Health Study conducted a study of 690 nurses and concluded that participants who were in the highest quintile of the diet score had on average 24% lower CRP levels as compared with those in the lowest quintiles [88].

Human experimental feeding studies:

Results from clinical trial studies have given contradicting findings. Six studies assessed whether there were significant associations between the Mediterranean Diet and sensitive markers of systemic inflammation for CRP. Esposito et al. wanted to determine the effect of MED on endothelial function and vascular inflammatory markers in 180 metabolic syndrome patients (99 men and 81 women). When comparing patients who consumed the intervention diet (cases) with the control diet (control), better adherence to MED was associated with lower levels of hs-CRP [89]. The PREDIMED (Prevención con Dieta Mediterránea) study compared three dietary interventions: MED with supplemental virgin olive oil (VOO),

MED with supplemental nuts, and a low-fat diet. Among 112 participants, the study found that CRP levels decreased only in the MED group given virgin olive oil [90].

Other studies confirmed the association between CRP levels and adherence to MED in individuals with metabolic syndrome. Estruch et al. demonstrated that the Mediterranean Diet plays an important role in decreasing inflammation by reducing lipid accumulation in atherosclerosis and diabetes patients. In the study, a low-fat diet (n = 257) compared with a Mediterranean Diet with those that consumed either free virgin olive oil, 1 liter per week (n = 257), or free nuts, 30 g/d (n = 258). The data showed that participants who were allocated to the Mediterranean Diet plus olive oil group were associated with a lower CRP concentration when compared with participants with a low fat diet and the Mediterranean Diet with olive oil groups [91]. Consistently, Viscogliosi et al. examined the associations between adherence to MED and the prevalence of metabolic syndrome. They found the MED score to be inversely associated with hs-CRP among 120 subjects [92].

Studies reported no association between MED and inflammatory biomarkers:

Five studies found no association with high adherence to MED and lowered risk of developing systemic inflammation by reducing CRP levels. The studies by Michalsen [93] et al, Ambring et al [94], Dai et al [95], Salvadó [96], and Rallidis et al [97] showed no strong or consistent association between the MED and inflammatory markers. Two hospitals recruited 101 patients with established coronary artery disease (CAD) as verified by coronary angiography after undergoing diagnostic coronary angiography to consume the MED diet for 12 months. CRP, fibrinogen, fasting insulin, homocysteine, serum lipids and plasma fatty acids were measured before and after the intervention. The study found that following the MED diet had no effect on inflammation and metabolic risk factors in CAD patients [93]. Healthy

individuals consumed either the MED diet or an ordinary Swedish diet for four weeks. While MED lowered the number of platelet and leukocytes and vascular endothelial growth factor, it did not change CRP levels between the two diets [94]. Moreover, an investigation of psychological, behavioral, and biological risk factors for subclinical cardiovascular disease using twins in The Twins Heart Study (THS) found that a high adherence to MED did not help reduce CRP after adjustment for total energy intake and other nutritional factors. These results suggest that the association between MED adherence and systemic inflammation is unlikely to be affected by shared genetic and environmental factors [95]. A study of Spanish men and women with a high risk of cardiovascular disease by Salvadó did not find any association between adherence to a Spanish Mediterranean diet and reduced inflammatory markers. Concomitantly, they did find an inverse association between the high Spanish MED and hs-CRP levels. Also, hs-CRP ranked the lowest in those categories with the highest consumption of olive oil and nuts and IL-6 with the consumption of fruits and cereals [96]. A Greek study by Rallidis did not show any effect of MED on hs-CRP, but they found that endothelial function such as flow-mediated vasodilatation and diastolic blood pressure improved after consuming a Mediterranean Diet for two months [97].

Dietary Approaches to Stop Hypertension (DASH)

The Dietary Approaches to Stop Hypertension (DASH) diet is a dietary pattern developed by the U.S.-based National Heart, Lung, and Blood Institute to prevent and control hypertension [98]. DASH diet is characterized by a high consumption of fruits, vegetables, whole grains, and low-fat dairy foods, meat, fish, poultry, nuts and beans, and is limited in sugar-sweetened foods and beverages, red meat, and added fats [99].

Evidence gathered from studies conducted approximately a decade ago indicated that the DASH diet helps lower the risk of several diseases [100]. In 1999, a study of 459 adults found that a DASH diet may be an effective alternative to drug therapy in hypertension. It may also prevent hypertension in African-Americans when compared to Caucasians [101]. Obarzanek et al. demonstrated that the DASH diet may help reduce coronary heart disease in 436 randomized controlled outpatients [102]. Two case-control studies found significant associations between adherence to a DASH diet and blood pressure levels among patients with and without hypertension issues when comparing DASH with two other dietary patterns [103, 104]. A randomized crossover study of 12 obese patients with high-normal to stage 1 hypertension and 12 lean normotensive volunteers found that following a DASH diet for four weeks raised antioxidant capacity, lowered blood pressure, and reduced oxidative stress [99]. Many studies have reported that a DASH diet may reduce the risk of contracting some cancers such as postmenopausal breast cancer [105] and colorectal cancer [71]; while the calcium in dairy products would help lower the risk of osteoporosis [105]. Wengreen et al. conducted a study to determine the associations between DASH and Mediterranean-style dietary patterns and age-related cognitive change in a prospective, population-based study. The study found that a higher adherence to DASH and MED was associated with higher levels of cognitive function in elderly men and women over an 11-year follow-up period [82].

Dietary Approaches to Stop Hypertension and Inflammation

In recent years, a rapidly increasing number of studies reported that the DASH diet contributes to a decrease of several risk factors such as triglycerides, systolic blood pressure, diastolic blood pressure, colorectal cancer, reduced insulin resistance,

and increase HDL cholesterol. All of these factors would support the role of the DASH diet in decreasing inflammation [71, 72]. A DASH diet improved neurocognitive function among 124 participants [106]. The DASH diet is considered an anti-inflammatory diet for diabetes patients because it helps to reduce liver aminotransferases and fibrinogen levels [107].

Human experimental feeding studies:

A randomized crossover intervention trial was done of two diets, a high-fiber (30-g/d) DASH diet or fiber-supplemented diet (30 g/d) for three weeks. Among 35 participants (18 lean normotensive and 17 obese hypertensive individuals), adherence to the DASH diet, including high fiber intake levels, helps to reduce CRP levels [108]. Similar results reported by Saneei et al. investigated the effects of the DASH diet on systemic inflammation markers in adolescents with metabolic syndrome. After six weeks of follow up among 60 post pubescent girls, CRP levels were reduced by the DASH diet among participants, but it had no effect on other inflammatory markers [109].

Two crossover clinical trials by Azadbakht et al. provide evidence of the effect of DASH on CRP levels. The first study was of 42 postmenopausal women with metabolic syndrome. These women consumed either a DASH diet, soy nut diet, or soy protein diet for 8 weeks. Red meat in the DASH diet (one serving/day) was replaced by soy protein in the soy protein diet and by soy nut in the soy nut diet. The study found that replacing red meat with soy protein and soy nut lowered CRP levels more than consuming a regular DASH diet [110]. The second study was of 60 patients diagnosed with type 2 diabetes at the Shaheed Motahari Hospital of Fooladshahr in Isfahan, Iran. The participants received either a control diet that included a

macronutrient composition of 50–60% carbohydrates, 15–20% protein, 30% total fat, and a 5% energy intake from simple sugars and DASH which included fruits, vegetables, whole grains, and low fat dairy products, or a diet low in saturated fat, total fat, cholesterol, refined grains, and sweets. The data suggests a beneficial effect of DASH adherence in these participants because the decrease in CRP plasma and other inflammatory markers during the DASH diet period was greater than that of the control diet [111].

Other observational studies have provided equally confusing results, with some findings suggestive, while others had statistically insignificant effects for DASH on CRP levels and others found no effects. A case-control study evaluated the association between inflammation levels and a low-fat/reduced-cholesterol diet versus the DASH diet. In this randomized study, 100 participants were assigned to receive either the DASH diet or the control diet for two weeks. The study found that the consumption of the DASH diet had no effect on CRP levels [112]. Similarly, Asemi et al. reported that the consumption of the DASH diet for four weeks in randomized controlled clinical trials of 32 pregnant women had no effect on CRP levels [113]. Another observational study by Shenoy et al. found no preventive effects from DASH on CRP in 81 (22 men and 59 women) participants with metabolic syndrome after consuming the DASH diet [114].

<div align="center">Fatty Acids</div>

Fatty acids are carboxylic acids with short, medium, and long chains, which are either saturated or unsaturated. Most naturally occurring fatty acids have an even number of carbon atoms, from 4 to 28 [115]. The structured name for a fatty acid is based on the number of double bonds and the number of carbons in the acyl chain [116]. Saturated fats (SFA) have no double bonds in the fatty acid chain. In contrast,

unsaturated fatty acids contain either one double-bound monounsaturated fat (MUFA) or more than one in polyunsaturated fat (PUFA) [117, 118]. Essential fatty acids foods are the main source [119] including for linoleic acid (LA) omega-6 (n-6) fatty acid, and α-linolenic acid (ALA) omega-3 fatty acid (n-3) [120].

Docosahexaenoic acid (DHA) is one of the major fatty acids in the brain. It plays an important role in the development of the human central nervous system [121]. There is a strong relation between a higher consumption of essential PUFAs and improved cognitive function [122]. Human studies found the high consumption of DHA increased IL-6 and IL-1 receptor antagonists which decreased levels of pro-inflammatory markers [123, 124]. In 2009, The Academy of Nutrition and Dietetics reported that adequate DHA/EPA fatty acids may delay the onset of Alzheimer's disease [125].

Fatty acids and Inflammation

Recent works highlight the importance of fatty acid consumption and inflammation levels. A growing body of literature shows strong correlations between SFA consumption and the inflammatory state of white adipose tissue [126]. It has been reported that a low consumption of SFA reduces the risk of CHD [127], liver disease [128], many metabolic disorders [129], all causes of death [130]. In 1965, Keys and his colleagues reported that a high intake of SFA and a low intake of PUFA increase deaths from coronary heart disease, cancer, and stroke. These findings lead to recommending higher PUFA consumption to replace SFA. In 2009, the American Heart Association (AHA) reported that a high intake of n-6 is safe and may be beneficial when it replaces with SFA [131, 132].

Omega-3 FAs make up a family of PUFAs. Omega-3 metabolism starts with α-alpha linolenic acid (ALA). ALA is the simplest member of this omega-3 and it

converts to Eicosapentaenoic acid (EPA) which forms prostaglandin (PGE3) and docosahexaenoic acid (DHA). Both PGE3 and DHA have anti-inflammatory effects. Biochemical studies have suggested that AA competes with EPA for the same set of enzymes to form the long chain of PUFA derivatives [123, 124]. Strong evidence suggests that high intake of omega-3 fatty acids increases fatty acid levels in human immune cells, which leads to an improved anti-inflammatory profile by changing mediator production and regulating immune response [121]. Animal experiments and clinical intervention studies show that EPA and DHA have varied anti-inflammatory effects by managing inflammation and autoimmune disease [133], modulating the types and the amount of eicosanoids and cytokines, as well as altering gene expression [134]. These effects are based on dosage, time, and baseline characteristics of the subjects. Also, epidemiological observations from case-control studies found that fish oils help to reduce the activity of chronic inflammatory diseases and it naturally mimics anti-inflammatory drugs [135-137].

Until now, we are still unsure if n-6 fatty acids are harmful, harmless, or helpful. Omega-6 fatty acids is another family of PUFAs. In 1985, the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine reported that fish consumption had dropped and vegetable oil consumption increased considerably [138]. Even then, scientists continued to debate over whether Americans and others on a typical Western diet are eating too much of n-6. Many epidemiological studies reported the negative effect of n-6 consumption on health, which causes increased risks of contracting several diseases [139-141]. Andoh reported that a higher consumption of a diet rich in omega-6 promotes immune responses by increasing the cytokine IL-6 level and limited mucosal damage [142]. Chapkin and his colleague used interleukin 10 (IL-10) knock-out mice to investigate

the association between n-6 and inflammation. The study concluded that chronic inflammation level was high in the group who consumed corn oil (n-6) than the other group who consumed fish oil (n-3) [143]. In Japan, a case control study of 111 patients reported that high intakes of n-6 was associated with coronary heart disease (CHD) incidence [144] because n-6 increases the production of ROS from inflammatory cells [145]. Two cross sectional studies provide evidence of higher consumption of n-6 that has pro-inflammatory effects among Nonalcoholic fatty liver disease (NAFLD) patients. The first study was in 45 NAFLD patients (cases) compared with a sample of 856 (controls), matched for sex and age. The results of that study suggest that increased n-6 intake may contribute to neuroinflammation [146]. The second study was in 349 volunteers from the Israeli National Health and Nutrition Survey. Diet history assessed by food frequency questionnaires (FFQ) demonstrated higher meat intake and a tendency of having a lower intake of fish rich in omega-3 in NAFLD patients [147].

Recently, researchers challenged the dogma of omega-6 as pro-inflammatory, because they report that omega-6 fatty acids have both anti-inflammatory properties and pro-inflammatory properties [131, 148, 149]. Relevant cell culture studies reported that omega-6 fatty acids have anti-inflammatory properties by inhibiting the production of interleukins, chemokines which reduces atherosclerosis progression [150]. Omega-6 has an anti-inflammatory effect on regulating PGE2 production from macrophages, which inhibits TNF-α synthesis [7] and lipoxins formation [9]. Likewise, two studies found that PPAR-alpha (PPARα) expression in pretreated cultured human endothelial cells and human aortic smooth-muscle cells were significantly expressing the anti-inflammatory effects of both n-6 (AA) and n-3 by suppressing nuclear factor-kB (NF-$_k$B) signaling [151, 152]. PUFAs, both n-6 (AA)

and n-3, have anti-inflammatory properties due to the unsaturated double bond that inactivates reactive oxidative species (ROS) and inhibits the interaction with NF-$_k$B [153, 154]. Concomitantly, human observational studies suggested that high plasma levels of omega-6 maintained a positive correlation to IL-10, which is the anti-inflammatory cytokine [155]. Meanwhile, human experimental studies reported that feeding healthy volunteers 7 times (15g/d) the usual intake of AA for 7 weeks had no effect on platelet aggregation, bleeding times, the balance of vasoactive metabolites, serum lipid levels, or immune responses [156, 157]. Likewise, when habitual dietary intake was investigated among healthy men and women, the combination of total n-6 and n-3 contributed to lowering the inflammatory biomarkers including TNF. Moreover, when participants consumed a high level of EPA, DHA, LA, and n-6 fatty acids did not suppress the effects of n-3 anti-inflammatory properties [158]. In Japan, two studies confirm that a high intake AA supplement had no effect on platelet function or any metabolic parameter [159] although it may have the ability to prevent CVD [160]. GLA is one type of omega-6 that has been studied for a while to explain the anti-inflammatory effects of omega-6 [161]. Moreover, some prospective cohort studies have not found significant associations between n-6 intake and hemorrhagic [162, 163], stroke or stroke mortality [164], and ischemic [162, 163, 165].

Fatty acid composition of the modern Western diet has changed. Typically the ratio of n-6: n-3 in the Western diet has been estimated to be 15:1 to 16.7:1 [166, 167]. High levels of n-6 intake could escalate in vivo susceptibility to low-density lipoprotein (LDL) oxidation that can promote vascular inflammation [168, 169]. Even though omega 3 has anti-inflammatory effects in humans, a high ratio of n-6: n-3 may increase pro-inflammatory cytokine production [170]. These changes might be a cause of the increase in inflammatory diseases [171, 172].

Until now, it's still hard to be sure that diet may reduce IBD cases, it has been proposed that a high incidence of IBD is related to a high ratio of n-6:n-3 [173]. Animal studies are used trinitrobenzene sulfonic acid (TNBS) rat models to investigate the effect of n-6:n-3 with colitis [139]. Using TNBS model studies demonstrated that a diet rich in safflower oil (n-6) rather than omega-3 rich foods including cod liver oil and perilla oil increases colonic ulceration damage and inflammation levels including Leukotriene B4 (LTB4)[1] levels [174-176]. Moreover, it has been proposed that consuming a diet with a high ratio of n-6:n-3 is related to the severity and the thickness of the inflammatory infiltrate [177] and it increases intestinal damage and inflammation during infection-induced colitis [173]. Fat-1 transgenic mice revealed that low ratio of n-6:n-3 reduces pro-inflammatory cytokines, IL-6, and IFNγ and decreases the incidence of colitis [178]. Moreover, a recent prospective cohort study in Denmark examined the high levels of n-6:n-3 ratio in adipose tissue in ulcerative colitis (UC) patients (57,053 men and women). They found that inflammation was the interacting factor between diet and disease progressions by increasing inflammatory responses [179]. In colonic biopsies, high levels of n-6:n-3 ratio regulate LTB4 that are pro-inflammatory lipid mediators that have been correlated with IBD [180, 181].

In Japan, a case control study of 111 patients reported that high intakes of n-6 was associated with CD incidence [144] because n-6 increases the production of ROS from inflammatory cells [145]. In 2003, a double-blind, randomized controlled trial enrolled patients to assess the effect of a low ratio of n-6:n-3 and atherosclerotic plaques progression. Fewer plaques and thin fibrous caps and signs of inflammation were found in patients who consumed high n-3 fatty acids. However, the high n-6

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[1] Leukotriene B4 (LTB4) is a leukotriene involved in inflammation.

group had more plaques and thick fibrous caps with no signs of inflammation [182]. Table 2.1 illustrates the studies that have investigated the relationships between fatty acids and inflammatory biomarkers.

To sum up, aggregate data from animal experiments, in vitro studies, and human observational and experimental feeding studies indicate that high n-6:n-3 ratios may lead to increased risk of contracting many diseases

Alzheimer's-Related Genes and Its Associations with Systemic Inflammation

Recent large genome-wide association studies (GWAS) have identified many genes/loci (CR1, BIN1, CLU, PICALM, MS4A4/MS4A6E, CD2AP, CD33, EPHA1, and ABCA7) that are associated with late-onset Alzheimer's disease (LOAD) [183]. Recent genetic data reveal that some risks of disease initiation, progression, and severity are linked to different gene alleles by affecting inflammation pathways. Gene diversity plays an important role in immunity, inflammation, and inflammatory disease [184]. For instance, Familial Cold Autoinflammatory Disease occurs as a result of single missense heritable mutation [185,186, 187].

Alzheimer's-Related Genes

Apolipoprotein E (APOE)

Apolipoprotein E (APOE) is a lipoprotein class that is found in chylomicron and intermediate-density lipoproteins (IDLs). APOE is essential to regulate triglyceride levels and metabolism and transport of cholesterol by binding to a specific receptor on the liver and peripheral cells and by the catabolism of triglyceride-rich lipoprotein constituents [188, 189]. Functionally, it contributes to neuronal development, regeneration, and repair in the central nervous system (CNS) [190, 191].

Even though APOE is considered the strongest genetic risk factor for AD, it still accounts for only 10–20% of LOAD susceptibility when combined with environmental factors [192]. The results of meta-analysis have firmly established that apolipoprotein E epsilon polymorphism leads to the generation of APOE 2, APOE 3, and APOE 4, which are coded by three alleles ε2, ε3, and ε4 [193]. Later, rs439401was found to be another type of APOE polymorphism that displays an association with AD [194]. Very few studies have investigated putative associations between APOE rs439401 and triglyceride traits [194-196].

Numerous data suggest that APOE has pro-inflammatory roles in the CNS [197, 198]. Brain biology and neurodegeneration studies suggest that APOE genotype ε4 has a role as an immunomodulatory agent and it has an effect on inflammatory mediators [199-201]. Other studies have focused on understanding the role of APOE in regulating acute inflammation [202] by increasing monocyte production of IL8 and TNF-α in human cells [203]. APOE and amyloid plaque association have been hypothesized to increase inflammation levels in the CNS by modifying beta-amyloid (Abeta)-induced glial activation [197]. Animal studies found that the APOE ε4 genotype is associated with cytokines by increasing pro-inflammatory cytokines IL-6 and TNF-α in mice that express human APOE [200, 204]. It has also been demonstrated that APOE deficiency in mice diminishes immune response, increases macrophage levels, and causes inflammation [205, 206].

Furthermore, other features work the implication of the anti-inflammatory role for APOE. APOE genotypes ε2/ ε2 are thought to reduce inflammation levels when researchers mixed neuronal-glial cultures from APOE deficient mouse pups and measured the secretion of TNFα after stimulation with lipopolysaccharide (LPS), and when they compared the inflammatory responses of targeted-replacement mice

expressing the human gene after intravenous administration of lipopolysaccharide [207] [200]. Negative effects on the inflammatory responses occurred as a result of isolating APOE ε4 from peripheral blood mononuclear cells [208].

BIN1

Bridging integrator 1 (BIN1) is located on chromosome 2q14.3. BIN1 encodes many isoforms of nucleocytoplasmic adaptor proteins. BIN1 has many roles in the human body such as tumor suppression, transcriptional regulation, DNA repair, and cytoskeletal organization [209]. BIN1 isoforms have many biological functions in the central nervous system. BIN1 may be involved in synaptic vesicle endocytosis and may interact with endophilin, dynamin, clathrin, and synaptojanin [210]. Many mouse genetic studies reported that BIN1 is associated with a decreased risk of chronic inflammation in the liver, pancreas, heart, prostate [211], inflammatory bowel disease [212] cancer [213] and AD [214]. There are several isoforms of BIN1 that are expressed in the brain. Knockout mosaic mice show that BIN1 reduced inflammation levels when they are aging [215]. Another study of aged mice reported the benefits effects of having BIN1 by reducing inflammation and cancer susceptibility [216]. Moreover, it has been found that BIN1 plays a role in cancer patients by suppressing the production of interferon-y (IFN-y), which is one kind of proinflammatory biomarker [217].

CLU

Clusterin (CLU) is a protein that can be found in the cytosol and is secreted under stress conditions, also known as apolipoprotein J [218]. A CLU gene may play a role in initiating the immune system because it is one of the phospholipid transfer proteins (PLTP), which links with apolipoprotein A-I – the major HDL protein [219]. It has several functions in neurodegenerative disorders, cell death, and tumor

progression [220]. CLU has a dual effect on inflammation. When CLU works as an anti-inflammatory, it enhances anti-apoptotic properties [221]. When CLU works as pro-inflammatory, it regulates a wide variety of stimuli that may increase the production of protein such as growth factors and cytokines [222, 223]. CLU has been linked to several diseases such as diabetes, aging, degenerative diseases [222], atherosclerosis [222, 224], and increased the risk of AD 8.2% [223]. It has been hypothesized that CLU might have a protective role in neuroinflammation and AD [224, 225].

CD2AP

CD2AP is an 80-kDa CD2 protein, which was initially replicated from a protein that works together with the CD2's cytoplasmic domain [226]. Extensive studies about human podocytes reported that low expression of CD2AP is associated with increased inflammatory biomarkers [227-230]. CD2AP plays an important role in the transportation of proteins and lipids within cells, and inflammation, and these are potential pathways for the development of Alzheimer's disease. Other studies suggest that this association might happen as a result of gene variants that contribute to late onset AD [226]. The gene CD2AP plays an important role as a cerebral inflammation regulator, a process that is associated with the brain being inhabited by viruses, in a dormant state. Scientists have found that there is a high presence of inflammatory-related genes in the brains of people suffering from Alzheimer disease. Essentially, the genes that are associated with the risk of Alzheimer's include CD2AP, which is also an inflammatory gene [231].

AGTR1

Angiotensin II receptor, type 1 (AGTR1) is the main product of aldosterone secretion [232]. It helps control blood pressure and the cardiovascular system

capacity. AGTR1 is responsible for mediating the cardiovascular system by affecting angiotensin II [233]. An experimental study revealed the proinflammatory effects of AGTR1 in the lungs of chronic antigen exposure to rats [230]. There was a significant relationship between CRP levels and AGTR1 polymorphisms that led to increased inflammation levels in 42-year-old women recruited from a population registry [232], a case-control community-who acquired pneumonia [258], a case-control community-who acquired pneumonia [234], and in a twin hypertension cohort [235].

MPP7

Membrane protein palmitoylated 7 (MAGUK p55 subfamily member 7) (MPP7) can be found in synapse adherence junctions [236]. MPP7 has been linked to increased inflammatory bowel disease, which may lead to malignant transformation of normal tissue [237]. A recent study found that MMP7 polymorphism probably helps manifestations within aspects of immune/inflammatory activity that are macrophage/monocyte-mediated [238] in ulcerative colitis [239]. The same result was observed in human [240] and mice epithelial cells [241].

MMP8

Matrix metallopeptidase 8 (neutrophil collagenase) (MMP8) is a part of the MPP7 family. MMP8 helps break down the extracellular matrix in normal physiological processes such as tissue remodeling in embryonic development and disease processes [242]. The main function for MPP8 is to degrade type I, II and III collagens [243]. It has been proposed that the absence of MMP8 in mice has been linked to increased lung inflammatory responses by modulating two major products S100A8 and S100A9, which activate macrophages regulating cell damage [244]. Strong evidence suggests that having MMP8 enhances inflammatory biomarkers

including TNF-α and IL-1β in metabolic syndrome [245], ischemic stroke [246], and cancer [242, 247].

TOMM40

Translocase of outer mitochondrial membrane 40 homolog (yeast) (TOMM40) is an essential protein importer in mitochondria. It forms channels to translocase the mitochondrial outer membrane (TOM) complex [248]. TOMM40 locus is located close in linkage disequilibrium with APOE on 19q13.2. This gene encodes an outer mitochondrial membrane translocase involved in the transport of amyloid-β and other proteins into mitochondria that have been involved in AD progression [249, 250]. Concomitantly, APOE-TOMM40 genotypes have been revealed to modify disease risk and age at onset of symptoms. TOMM40 has been linked to CRP and triglyceride levels in Australian families [251]. TOMM40 was found to have a pro-inflammatory effect in metabolic syndrome of 85,500 participants from 14 large epidemiological studies within the Cross Consortia Pleiotropy Group [252], and in the Candidate gene Association Resource (CARe) study and race-combined meta-analyses that included 29,939 additional individuals of European descent from CARe, and the Women's Health Initiative (WHI) [253].

CR1

Complement receptor 1 (CR1) can be found on leukocytes, glomerular podocytes, splenic follicular dendritic cells, and erythrocytes [254]. It encodes a monomeric single-pass type I membrane glycoprotein. CR1 helps to mediate and activate cellular binding to immune complexes and particles by activating T-cells [255]. CR1 has been associated with autoimmune and inflammatory disorders in the pathophysiology of a several diseases as pro-inflammatory [255-258] including AD [259-261].

CD33

CD33 or Siglec-3 is a trans-membrane receptor expressed on cells of myeloid lineage and sometimes can be found on lymphoid cells [262, 263]. CD33 inhibits cellular activity because it contains immunoreceptor tyrosine-based inhibitory motifs that activate the intracellular portion. CD33 is considered as an immunoglobulin superfamily because it has immunoglobulin domains (one IgV and one IgC2 domain) that affect the extracellular portion in cells [264]. Many studies have shown that CD33 is associated with an increased risk of AD in a Caucasian population. A new study among the Chinese Han population revealed that a higher AD risk is associated with allele T in MS4A6A and allele C in CD33 [192, 265]. Later, inflammation was proposed as one way that CD33 affects AD [266].

PICALM

Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) is a clathrin assembly protein that recruits adaptor protein complex 2 (AP2) and clathrin [267]. Even though PICALM polymorphisms are associated with the risk of Alzheimer's disease [268], this association is still far weaker than APP, PSEN1, PSEN2, and APOE [267].

MS4A6A

Membrane-spanning 4-domains, subfamily A, member 6A (MS4A6A) is a gene that encodes a member of the membrane-spanning 4A gene family [265]. Hematopoietic cells and nonlymphoid tissues are the unique expressions for MS4A6A in human. MS4A6A has different protein isoforms due to unusual splicing [269]. Membrane-spanning 4-domains, subfamily A, member 4E (MS4A4E) is a type of the MS4A gene family and it encodes at least four transmembrane domains C- and N-terminal cytoplasmic domains that are encoded by distinct exons. MS4A6A has an

effect on T cell levels in humans [270] which may explain the proinflammatory effects in northern Han Chinese [266].

ABCA7

ATP-binding cassette, sub-family A (ABC1), and member 7 (ABCA7) are associated with the superfamily of ATP-binding cassette (ABC) transporters [271]. ABC proteins transport various molecules across extra- and intra-cellular membranes. It consists of seven distinct subfamilies (ABC1, MRP, OABP, MDR/TAP, ALD, GCN20, and White). The function of this protein is still unclear, however, the gene expression is related to lipid homeostasis especially cholesterol in cells of the immune system [272]. It has been believed that cytokine levels such as IFN-γ, IL-1β and platelet-derived growth factor (PDGF) may decrease ABCA7 expression. However, other cytokines such as IL-10 have been shown to increase ABCA7 expression [273, 274].

DTNA

Dystrobrevin, alpha (DTNA) is a dystrophin-associated protein complex (DPC) and it has been identified as having different isomers when mutated [275]. This gene was found to be involved in the formation and stability of synapses and the clustering of nicotinic acetylcholine receptors. Studies had shown that DTNA gene polymorphisms are related to left ventricular defects when patients had congenital heart defects [275].

HTR2C

5-Hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (HTR2C) is a coupled receptor for 5-hydroxytryptamine and it is considered a neurotransmitter. In certain areas of the brain, this gene inhibits dopamine and norepinephrine releases by binding serotonin [276].

EPHA1

EPH receptor A1 (EPHA1) is a member of the protein-tyrosine kinase family in the ephrin receptor subfamily. EPHA1 has been found in some human cancer cell lines and has been associated with carcinogenesis [277]. EPHA1 has been linked to inflammation as it plays a role in apoptosis [201, 278]. It has been reported that EPHA1 plays an important role during endothelial cell activation by enhancing proinflammatory gene expression in mouse and human atherosclerotic plaques [279].

SORCS1

The sortilin-related VPS10 domain containing receptor 1 (SORCS1) is one of the vacuolar proteins sorting 10 (VPS10) family members. It mediates intracellular protein trafficking and sorting [280]. It has many functions in a developing and maturing central nervous system, and it displays neuropeptide receptor activity [281]. SORCS 1 has been linked to AD pathogenesis by increasing Aβ production [282].

PPP3R1

Protein phosphatase 3, regulatory subunit B, and alpha (PPP3R1), calcium dependent, have many functions such as by being a calmodulin stimulated protein phosphatase, and a regulatory subunit of calcineurin [283]. Mutation in this gene has been linked to increasing AD risk by affecting calcium signaling pathways [284].

MAPT/STH

STH is known as MAPT. The transcripts of MAPT can be found in the nervous system and it is expressed differently depending on the neuron type and cell maturation. Studies have shown that MAPT is related to many neurodegenerative disorders such as Pick's disease, front temporal dementia, corticobasal degeneration and progressive supranuclear palsy, and AD [285-287]. STH is considered to be like a tau protein and is linked to many neurodegenerative disorders [288]. In 2008, a study

conducted in China found that a polymorphism in STH may increase neuroinflammation and abnormal phosphorylation of TAU proteins in AD patients [289]. It has also been proposed that mutation in MAPT/STH may cause front temporal dementia [290].

In conclusion, GWA is a great technique to discover novel susceptibility gene/loci for AD. All of these genes (APOE, BIN1, CLU, CD2AP, AGTR1, MMP8, MPP7, TOMM40, CR1, CD33, PICALM, MS4A6A, MS4A4E, ABCA7, DTNA, HTR2C, EPHA1, SORCS1, PPP3R1, MAPT/STH) have been associated with AD which may facilitate new research in human genetics and genomics with biological insights and direct clinical benefit.

Table 2.1: Studies reporting the relationship between fatty acids and inflammatory biomarkers.

Fatty acids	Type	Inflammatory types	Published evidence between fat acids and inflammatory cytokines	
			Statistically significant P-value <0.05	Statistically Not significant P-value >0.05
Pentadecanoic acid	SFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to ant-inflammation	
Palmitic acid	SFA	Pro-inflammatory	[291-299]	[300, 301]
		Anti- inflammatory	No references found related to ant- inflammation	
Margaric acid	SFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	[302-304]	
Stearic acid	SFA	Pro-inflammatory	[294, 298, 299, 305-307]	[300, 308]
		Anti- inflammatory	[309]	
Arachidic acid	SFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to ant-inflammation	
Behenic acid	SFA	Pro-inflammatory	[298]	
		Anti- inflammatory	No references found related to ant-inflammation	
Lignoceric acid	SFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to anti-inflammation	
Palmitoleic acid	MUFA	Pro-inflammatory	[299]	
		Anti- inflammatory	[310-314]	
Oleic acid	MUFA	Pro-inflammatory	[315, 316]	[317, 318]
		Anti- inflammatory	[126, 310, 319-321]	
Gondoic acid	MUFA	Pro-inflammatory	No references found related to ant-inflammation	
		Anti- inflammatory	No references found related to pro-inflammation	
Erucic acid	MUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to ant-inflammation	
Nervonic acid	MUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to anti-inflammation	
Vaccenic acid-Trans	TFA	Pro-inflammatory	[316]	[322, 323]
		Anti- inflammatory	[324, 325]	
Linoleic acid (LA)	PUFA	Pro-inflammatory	[289, 291-293, 320, 326, 327]	[296, 328, 329]
		Anti- inflammatory	[330, 331]	
α-Linolenic acid (ALA)	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	[126, 293, 320, 330-333]	

Eicosadienoic acid	PUFA	Pro-inflammatory	[334]	
		Anti- inflammatory	No references found related to ant-inflammation	
Dihomo-γ-linolenic acid (DGLA)	PUFA	Pro-inflammatory	[335]	[317]
		Anti- inflammatory	[336]	
Arachidic acid	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to ant-inflammation	
Eicosapentaenoic acid (EPA)	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	[126, 293, 320, 330-333]	
Arachidonic acid	PUFA	Pro-inflammatory	[136, 292, 335, 337]	[296, 338, 339]
		Anti- inflammatory	No references found related to anti-inflammation	
Adrenic acid	PUFA	Pro-inflammatory	No references found related to pro-inflammation	[317]
		Anti- inflammatory	No references found related to anti-inflammation	
Docosapentaenoic acid n-3	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	[340-343]	
Docosapentaenoic acid n-6	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	No references found related to anti-inflammation	
Docosahexaenoic acid (DHA)	PUFA	Pro-inflammatory	No references found related to pro-inflammation	
		Anti- inflammatory	[121, 126, 292-294, 301, 329, 330, 335, 337, 344-347]	

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CHAPTER 3

THE ROLE OF THE DIETARY APPROACH TO STOP HYPERTENSION (DASH)

AND MEDITERRANEAN DIETARY PATTERNS IN SYSTEMIC

INFLAMMATION

IN THE CACHE COUNTY MEMORY STUDY

Abstract

Objective: To evaluate whether healthy dietary patterns, defined by the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean dietary patterns (MED), are associated with a reduced level of systemic inflammation as indicated by levels of inflammatory CRP in plasma in a prospective, population-based study.

Design: Participants included 1,713 men and women ≥65 y at baseline of age who were residents of Cache County, Utah, in 1995. Diet-adherence scores were computed by summing across the energy-adjusted rank-order of individual food and nutrient components and categorizing participants into quintiles (Q) of the distribution of the diet accordance score. Multiple logistic regression models were used to examine the risk of elevated CRP level (> 3.0mg/L) across increasing quintiles of accordance dietary scores and individual food components that comprised each score.

Results: High adherence score to the DASH and MED dietary patterns were similarly associated with a reduced risk of elevated CRP (odds ratio for Q5 vs Q1: DASH (aOR= 0.74, 95% CI 0.53- 1.05; MED: aOR= 0.73 (0.52- 1.0)). This association appeared stronger among overweight and obese participants (DASH: aOR= 0.65 (0.41- 1.0), p-trend = 0.027; MED: aOR= 0.55 (0.35- 0.8), p-trend= 0.018) than among normal weight (DASH aOR= 0.86 (0.52- 1.4), p-trend= 0.46; MED aOR= 0.98 (0.58- 1.6), p-trend= 0.916. Food component dietary scores associated with reduced risk of elevated CRP included nuts and legumes (DASH), legumes (MED),

fruits (MED), and high-fat dairy (MED) was associated with an increased risk; these food associations were generally not observed among the low-BMI participants.

Conclusions: The DASH and Mediterranean dietary patterns may play an important role in reducing systemic inflammation, especially in overweight and obese elderly persons.

Introduction

Systemic inflammation is a risk factor for the development of Alzheimer Disease (AD) [1]. AD is the most common form of dementia among aging men and women worldwide [2]. Studies in elderly patients with mild cognitive impairment (MCI), AD and normal elderly have suggested that measuring peripheral inflammatory markers including tumor necrosis factor α (TNF-α) in AD patients helped to detect early progression of both MCI and AD [3, 4]. Despite the complicated etiology of inflammation, C-reactive protein (CRP) is one of the strongest and most commonly reported inflammatory biomarker [5]. Concomitantly, CRP has been linked to many diseases including metabolic syndrome, diabetes, cardiovascular [6], and AD [7].

Dietary quality scores method have been used widely to assess the relationship between diet adherence and CRP levels [8-10]. Two dietary quality scores of interest are the Mediterranean diet (MED) and the Dietary Approach to Stop Hypertension (DASH) scores. The Mediterranean diet is a traditional dietary pattern from different countries bordering the Mediterranean Sea. MED diet is characterized by a high consumption of fruits, vegetables, whole grains, full-fat dairy foods, meat, fish, poultry, nuts and beans. MED diet is also limited in sugar-sweetened foods and beverages, red meat, and added fats and includes a moderate consumption of alcohol [11]. Mediterranean diet is usually higher in n-3 (α-linolenic acid) and lower in n-6

(linoleic acid) which may explain the anti-inflammatory effects of MED diet. Olive oil is the primary fat in this diet [12]. Much epidemiologic research indicates that MED diet adherence was associated with beneficial health outcomes including improved quality of life [13-15], reduction in mortality risk, and major chronic disease incidence [16, 17] such as cancer, cardiovascular mortality, Parkinson's disease [18], and Alzheimer's disease [14, 19-21].

The Dietary Approaches to Stop Hypertension (DASH) was developed to lower and control hypertension by Appel and others and funded by the U.S.-based National Heart, Lung, and Blood Institute [22]. It includes a high consumption of fruits, vegetables, low fat and nonfat dairy, beans and nuts, with small amounts of lean meats, fish, poultry, and grains (at least 3 servings of whole grains per day), low intake of fats and sweets, and sodium intake should be limited to 2,300 mg each day [22, 23]. Evidence gathered from studies conducted approximately a decade ago indicated that the DASH diet helps lower the risk of several diseases including hypertension [24], coronary heart disease [25], stroke [24], cancer [26], osteoporosis [27], cognitive function [28], kidney diseases [29], bone health by reducing bone turnover [30], and AD [21, 31]. In the current study, we examined the associations between MED and DASH dietary adherence scores and systemic inflammation levels as indicated by levels of inflammatory CRP, using the data from the Cache County Memory Study (CCMS).

Methods

Study Participants and Data Collection

The Cache County Memory Study is a prospective cohort study among elderly who were 65 years old and older in 1995 and who were permanent residents of Cache County, Utah. This population is largely non-Hispanic White and the genetic makeup

is mostly from Northern European ancestry. The institutional review boards of each collaborating site at Utah State University, Duke University Medical Center, and The Johns Hopkins University approved the protocol of the study.

On January 1, 1995, trained personnel from Center for Epidemiologic Studies at Utah State University visited and interviewed 5,092 residents representing a 90 percent response rate in the baseline interview. The baseline interview included information about demographic characteristics, health history, and family history of dementia, use of medications, alcohol, tobacco, other lifestyle factors, and extensive cognitive testing. Reassessments of this study were completed in different years with a decline in the screening sample size: Wave 2, 1998-1999, with 3,411; Wave 3, 2002-2003, with 2,344; and Wave 4, 2005-2006, with 1,137. Details of the study protocols have been previously published [32].

Diet Assessment

A food frequency questionnaire (FFQ), patterned after the Nurses' Health Study [33, 34], was used to assess usual dietary intake at the Wave 3 interview examination [21]. Many studies have shown that FFQ is an appropriate tool for populations of different demographic characteristics and different ages [34]. The Food Processor Program (ESHA Research, Portland) was used for the nutrient analysis. All nutrients from foods were adjusted for total caloric intake via the regression-residual methods of Willett [35]. Nutrient intakes from supplements were added to energy adjusted nutrient intake levels from food to obtain an accurate measure of total nutrient intake.

In Wave 3, the FFQ included 150 food items with specified serving sizes described by using usual portions (e.g., 1 orange, 1 slice of bread) of the servings commonly consumed in this study population. For each food item, participants

indicated their average frequency of consumption over the past year in terms of the specified serving size by checking 1 of 9 frequency categories ranging from "almost never, <1 per month" to "≥6 times/d." Participants were asked to report the name brands of some food items such as cereal and margarine. Also, participants were asked to list any food items that were not mentioned in the FFQ and report the serving size of that food and how many times they had it. The last part of the FFQ includes questions about following a specific diet such as: Do you follow a special diet? How many years do you follow it? Was the diet prescribed by a doctor? How many years have you been following this diet? What kind of diet did you follow?

Mediterranean diet and DASH Assessment

Based on the nutrient and food components, the Mediterranean diet (MED) and DASH diet adherence scores were computed. The Mediterranean diet contained eight components: a high intake of vegetables, fruits, grains, fish, legumes, and a ratio of monounsaturated fatty acids to saturated fatty acids (MUFA:SFA), low intakes of meat and meat products, and high-fat dairy products. Alcohol consumption was not used to define the MED diet score because of low rates of alcohols consumption in the population. The DASH diet adherence scores were contained the following components: a high intake of vegetables, fruits, nuts and legumes, whole grains, and a low intake of fat from dairy products, sodium, sweetened beverages, and red and processed meats. Both diet components were selected to represent food groups targeted in the DASH diet [36] and the Mediterranean diet [16] as described previously by Wengreen [21].

Participants were categorized based on their consumption of each food component in both the Mediterranean and DASH diets including: fruits, vegetables, whole grains, total grains, full-fat dairy foods, nuts, legumes (nuts and legumes),

MUFA/SUFA ratio, and fish (Table 6). Based on the adopted method used by Wengreen et al., (Table 3.1). For each component, participants were ranked based on the distribution of food or nutrient component intake levels. Mediterranean diet adherence and DASH scores were determined by summing across the ranked scores of each relevant nutrient and food component. The sum score of the ranked scores of each relevant nutrient or food component defined the diet adherence scores. The score range for each food group is from 1-5. Therefore, higher values indicate greater adherence to the Mediterranean diet and DASH. Positive scoring meant that participants who consumed the lowest amount in the food group received a low rank score of 1, and participants who consumed the highest amount in the food group received the highest rank score. Inverse scoring study samples were arranged in the opposite order based on their intake levels of sweetened beverages, sodium, red and processed meat, and full fat dairy food. Negative scoring meant that the participants who consumed the lowest amount received the highest rank score; while participants who consumed the highest amount received a rank score of 1 [37, 38].

CRP assessment

Blood samples were collected and assayed for CRP from participants in Wave 3 at McKay Dee Hospital Laboratory, Ogden, UT by Dade Behring BNII (BN for Behring Nephelometer) for high-sensitivity CRP (hs-CRP) in 2002. Dade's nephelometry method has been considered for quite some time as a gold standard for these tests in the laboratory industry [39]. Many large reference studies refer to the Dade BNII assay that uses particle enhanced immunonephelometry. Dade was one of the first vendors to receive FDA approval for cardiac marker claims for their sensitive CRP assay [40]. The method uses polystyrene particles coated with mouse monoclonal antibodies to CRP that are agglutinated when mixed with samples

containing CRP [41]. The intensity of the scattered light in the nephelometer depends on the CRP content of the sample and, therefore, the CRP concentration. Typically, expected values for healthy individuals are found to be < 3.0 mg/L, or < 0.3 mg/dL [42]. The measuring range is determined by the lower limit of the reference curve and depends on the concentration of the standard used. The typical limit of detection for the method was 0.175 mg/L or 0.0175 mg/dL. The upper level of detection was typically 1500 mg/L or 150 mg/dL. We defined elevated CRP as values >3.0 mg/L.

Statistical Analyses

SPSS version 22.0 was used for statistical analysis. The Analysis of Variance (ANOVA) test for continuous variables and Chi-square test for categorical were used to evaluate differences between quintiles of diet scores (Tables 3.2 and 3.3).

Logistic regression analyses were used to evaluate the risk of elevated CRP (>3.0 mg/L) by quintiles of each dietary pattern score with quintile 1 as the reference category while controlling the potential confounding variables. Obesity is associated with systemic inflammation [43-45]; thus, we further examined whether the diet-inflammation association was different among overweight and obese versus non-overweight (body mass index ≥25 versus <25 kg/m2). Potential confounding variables included in the model were gender (male, female), age (years), body mass index (BMI weight in kilograms/ height in meters2), educational level (less than high school, high school, college and graduate), drinking and smoking habits (never, former, current); health variables included diabetes (no, yes), stroke (no, yes), and heart attack (no, yes), multivitamin and minerals use (yes vs. no), APOE genotype (no e4, 1 or 2 e4). Participants with no dementia (n= 154) were excluded from all analyses. Reported p-values are two-sided, and type I error rate for statistical significance was 0.05.

Results

The range of rank-order DASH and Mediterranean diet scores was 1,602 - 14,049 and 2,033 - 13,525, respectively. The DASH diet scores and Mediterranean diet scores were positively correlated (r = 0.512, p-value <0.001). Participants in the highest quintile of DASH or Mediterranean diet scores were more likely to be women, more educated, less likely to have ever smoked or drank alcohol than were subjects in lower quintiles of either score. Participants in the highest quintile of the DASH or Mediterranean diet scores consumed less total fat, saturated fat, and cholesterol than did subjects in the lowest quintile of either diet score. Moreover, participants in the highest quintile of the DASH or Mediterranean diet scores consumed more fiber, vitamin C, folate, and vitamin B6, than did subjects in the lowest quintile of either diet score. The pattern of vitamin B12 intake was different between the two diet scores; no differences were observed across quintiles of the DASH diet score (P = 0.218), but vitamin B12 intake was lower in quintiles 4 and 5 compared to the lower quintiles of the Mediterranean diet score (P = <0.001). Subjects in the highest quintile of either accordance score consumed more potassium, magnesium, and zinc than did subjects in lower quintiles. Calcium intake increased across increasing quintiles of the DASH score, but the pattern was the opposite for the MED quintiles. An increasing quintile of the DASH diet but not Mediterranean accordance scores was associated with decreasing sodium intake. An increasing quintile of the Mediterranean diet but not DASH diet accordance scores was associated with increasing omega-3 and omega-6 fatty acid intake. There was no association between DASH and MED scores with age, APOE genotype, diabetes, or stroke. The heart attack was significantly associated with the Mediterranean diet but not with the DASH diet. Conversely, CRP

and multivitamin and mineral use was significant with the DASH diet but not with the Mediterranean diet (Tables 3.2 and 3.3).

Logistic regression analyses were used to evaluate the association between DASH and MED diet scores and elevated CRP levels (>3.0 mg/L). After controlling for covariates, The DASH diet score and MED diet score were similarly associated with a reduced risk of elevated CRP levels adjusted OR (aOR) and 95% confidence intervals (CIs)) for Q5 vs Q1: DASH (aOR=0.74 [95%CI 0.53- 1.05]30); MED (aOR=0.73 [95%CI 0.52- 1.0]). Nuts and legumes (DASH) and legumes (MED) were associated to reduce the risk of elevated CRP (aOR=0.72 [95%CI 0.51- 1.0]) and (aOR=0.75 [95%CI 0.54- 1.0]), respectively. Full fat dairy (MED) was associated with increased risk of elevated CRP (aOR=1.30 [95%CI 0.99- 1.9]), shown in Table 3.4.

Because obesity is associated with inflammation, we stratified the data by BMI to examine whether the associations between diet patterns and CRP differed in BMI strata. Mean plasma CRP concentrations were found in overweight and obese participants compared to non-overweight participants by using multiple logistic regression (Table 3.5) and (Table 3.6). Among overweight and obese persons there were significant decreases in plasma CRP across increasing DASH quintiles (aOR for quintile 5 vs. quintile 1= 0.65 [95%CI 0.41- 1.0]), MED (aOR = 0.55 [95%CI 0.35- 0.89]), nuts and legumes (DASH) (aOR = 0.60 [95%CI 0.38- 0.94]), legumes (MED) (aOR = 0.59 [95%CI 0.38- 0.93]), fruits (MED) (aOR = 0.71 [95%CI 0.45- 1.1]). Full fat dairy (MED) (aOR = 1.4 [95%CI 0.96- 2.3]) was associated with increased CRP plasma across quintile 5 vs. quintile 1. In non-overweight and non-obese participants, there was no association between plasma CRP and DASH and MED and their components.

Both MED and DASH scores were positively correlated with carbohydrate, fiber, total sugar, monosaccharide, disaccharide, vitamin B1, and vitamin B6, vitamin C, folate, pantothenic acid, copper, iron, magnesium, manganese, potassium, and zinc. The scores of MED but not DASH were positively correlated with intakes of vitamin B3, selenium, omega 3, and omega 6; the scores of DASH but not MD were positively correlated with phosphorus and calcium. Also, all three diet indices were negatively correlated with total fats, saturated fats, monounsaturated fats, cholesterol, vitamin B2, and caffeine. MED but not DASH scores were negatively correlated with intakes of total calorie intake, vitamin B12, calcium, and omega6:omega3 ratio; sodium was the only nutrients that are correlated negatively with DASH score (Table 3.6).

While the associations between DASH and MED diet patterns and reduced risk of elevated CRP appeared to be present only in overweight and obese persons and not among normal weight persons, there was not a significant multiplicative interaction between these diet patterns and CRP elevation ($p > 0.05$).

Discussion

Diet may influence the risk of Alzheimer's disease through its effects on systemic inflammation [46]. Overeating of certain specific dietary components is an important factor that should be considered in inflammatory processes [43, 47]. We report a reduction in risk of having a high level of CRP among overweight and obese elderly Utah study participants who were free of dementia in the highest versus lowest DASH and MED quintiles. A higher consumption of nuts and legumes, included in the DASH score, and legumes, included in the MED score, were the food items most strongly associated with a reduced risk of elevated CRP. Other individual food items appeared to contribute to the protective effect of both patterns particularly fruits and

vegetables. Conversely, higher consumption of full fat dairy was associated with an increase in CRP level.

Evidence gathered from studies conducted approximately a decade ago indicated that obesity plays an important role in the inflammation [43, 48]. The initiation step of inflammation in obesity starts with overeating that activates metabolic signals in adipose tissues, causing the increased production of bioactive molecules called adipokines [49]. Adipokines are cytokines (small proteins) that function as hormones and growth factor and influence inflammatory cells such as macrophages. The main function of adipokines is to regulate food intake, glucose and fatty acid metabolism, and energy expenditure [50]. Then, low grade inflammation causes changes in macrophages in the adipose and muscle tissue of obese individuals, which encourages pro-inflammatory responses and disturbs the normal physiological function [43, 51]. Over time, nutrient excess distresses the immune cell responses from metabolic cellular signals and reinforces inflammatory pathways, which cause unresolved chronic inflammation [43]. In normal conditions, feeding induces a low level of inflammation, but after the nutrients are metabolized inflammation levels diminish. Compared with lean persons, obese persons tend to consume high calorie food causing high fat deposition in abdominal fat and fatty liver. Thus, the resolution of inflammation become less efficient which activates adipokines activity and increase cell death. Consequently, the production of inflammatory mediators increases including interleukin 1β (IL-β), TNF-α, and CRP [43, 52-55]. Because of the previous evidence regarding the relationship between obesity and inflammation, we examined the relationship between DASH and MED dietary patterns adherence and CRP levels among the group that we thought more vulnerable and susceptible to inflammation that are overweight and obese participants.

The Mediterranean diet (MED) is a modern nutritional recommendation inspired by the way of eating traditional foods and drinks in Mediterranean olive grove areas [56]. This diet is rich in fruits, vegetables, legumes, and complex carbohydrates, with a moderate consumption of fish. The main source of fat is the consumption of olive oil and a low-to-moderate amount of red wine during meals [57]. The conceptual origins of the "Mediterranean Diet" in human studies were expanded to reflect the typical dietary patterns followed mainly in Greece, Spain, and Southern Italy [58]. In the early 1960s, the Seven Country Studies (SCS) was the first to recognize the health benefits of MED diet. SCS participants were from the United States, Japan, Italy, Greece, Netherlands, Finland, and Yugoslavia. The SCS team found low rates in the prevalence of coronary heart disease and cancers [58].

Our findings on the association between MED adherence and CRP were partly supported by previous human observational studies. A growing body of evidence suggests that Mediterranean diets could serve as an anti-inflammatory dietary pattern, which could help in fighting diseases that are related to chronic inflammation, including cardiovascular disease, metabolic syndrome diseases [59], and cognitive function [37]. Longitudinal studies reported a 3.2-20% reduction in CRP level among participants that consumed high levels of MED [60-62]. A significantly lower CRP level was found in three different populations including 180 metabolic syndrome patients, 690 nurses from The Nurses' Health Study, and 112 participants from PREDIMED (Prevención con Dieta Mediterránea), when comparing patients that consumed the intervention diet (cases) with the control diet (control) [10, 63, 64]. Two more clinical trials among individuals with metabolic syndrome participants have been conducted to estimate the prevalence of metabolic syndrome show that high consumption and strong adherence score to a Mediterranean diet had

significantly lowered pro-inflammatory CRP levels [65, 66]. However, other findings from human observational studies have been inconsistent. Five studies reported no preventive effect from strong adherence to MED diet on inflammatory biomarkers. Two Cohort studies found that high consumption of MED diet affects inflammatory markers TNF-α and IL-6 with no change in plasma levels of CRP [57, 67]. A study conducted in Spain, Greece, and Sweden showed no strong or consistent association between the Mediterranean Diet and inflammatory markers [68]. A crossover clinical trials from Spain, Greece, and Sweden showed no strong or consistent association between the Mediterranean Diet and inflammatory markers [69-71]. Another population-based case-control study using data from patients with coronary artery disease also did not reveal reduced CRP levels among these patients [72].

Even though a significant association between DASH accordance and the sensitive biomarker CRP was found in our study, studies on the association between DASH and CRP levels have produced mixed results. The DASH diet found in many studies to decrease inflammation levels by decreasing blood triglycerides, systolic blood pressure, diastolic blood pressure, colorectal cancer, insulin resistance, and increased HDL cholesterol [73, 74] due to dietary pattern components. The DASH diet is considered an anti-inflammatory diet for diabetes patients because it helps reduce liver aminotransferase and fibrinogen levels [75]. King et al. and Saneei et al. both reported a significant reduction of CRP levels when DASH was followed for three weeks [76] and for six weeks, respectively [77]. Two crossover clinical trials have been conducted to examine the effect of metabolic syndrome and diabetes reported the beneficial effect of DASH adherence in these participants because of the decrease in CRP plasma and other inflammatory markers when was DASH consumed more [78, 79]. In contrast, Asemi et al. found that consumption of the DASH diet and

a control diet for four weeks for randomized controlled clinical tests of 32 pregnant women had no effect on CRP levels [80]. Similarly, an observational study did not reveal reduced CRP levels among participants with metabolic syndrome [81].

The mechanisms by which the DASH and MED diets might affect CRP are unknown. Nuts and legumes were the food group with the strongest anti-inflammatory association in our study. Many health benefits have been reported for legumes on blood lipids [82], low glycemic index [83]. Legumes include dried beans, peas, lentils, tofu, soybeans, and green beans, all of which are sources of dietary fiber and resistant starch, which are rich in proteins, oligosaccharides, dietary fiber, potassium, calcium, and magnesium, polyunsaturated fatty acids, and phytochemicals. Legumes are also good sources of L-arginine (a precursor of nitric oxide) and polyunsaturated fatty acids, which have anti-inflammatory effects [84, 85]. Many studies did not report an inverse association between high legume consumption and lower CRP levels [86-88], whereas one crossover study resulted in a reduction of CRP [89]. In 2015, a meta-analysis of eight studies with 464 participants reported that high consumption of non-soy legumes reduced CRP levels and had a significant effect on CRP in parallel studies [90]. Nuts are a good source of fiber, phenolic compounds and other anti-inflammatories. Nuts are also rich in unsaturated fatty acids and contain sizeable amounts of L-arginine, which is a precursor of the endogenous vasodilator nitric oxide [91]. Nuts have been linked to reducing inflammatory biomarkers. A cross-sectional study of 6,050 participants including Americans age 45–84 years report that high consumption of nuts was associated with lower CRP levels among the Multi-Ethnic Study of Atherosclerosis [92]. The same result was observed in 339 men and 433 women age 55-80 years at high cardiovascular risk [91]. Few studies report an association between the combination of nuts and legumes, the food group used in the

DASH score, and CRP. A systemic review of cohort studies found that high consumption of the combination of nuts and legumes helps to reduce the risk of depression [93]. Cross-sectional data from diabetes-free female participants in the Nurses' Health Study of 3690 female age 30-55 concluded that nuts and legumes replacement for unprocessed red meat reduces inflammatory biomarkers CRP but after adjustment for BMI, the association did not demonstrate any significant difference [94].

In the present study, we found an association between increasing of full fat dairy, which is a negatively-scored MED component and elevated CRP levels similarly in overweight and obese and non-overweight and obese participants. Full fat dairy includes whole milk, chocolate milk, ice cream, cheddar and other hard cheese. In 2010, dairy consumption was associated with improved inflammatory profile by lowering inflammatory biomarkers [95]. In 2013, Kratz et al. reported that the beneficial effect of high fat dairy is still unclear, however, low fat dairy, which includes milk, yogurt, frozen yogurt, and cottage cheese, is related to many health benefits especially in metabolic syndrome markers including diabetes and blood pressure [96]. No previous study, to our knowledge, has reported an association between full fat dairy and CRP level. Da Silva et al. reported a correlation between adherences to dairy, which are composed of high and low levels of fat with CRP levels; the data suggest that strong adherence to dairy increases CRP levels. Concomitantly, the data reported that due to the study design, there was no causal relationship found between dairy intake and CRP levels [97].

To our knowledge, this is the first study that examines the multiplicative interaction between DASH and MED diet patterns and reduced risk of elevated CRP. Thus, further studies are needed to confirm our results.

The strength of the present population-based study is that the Cache County Memory Study (CCMS) is a large population-based study of white non-Hispanic elderly men and women. The Cache County Memory Study includes the repetitive detailed assessment of anthropometric and physiological variables at mean age of 74 at baseline for the same individuals in different subsets of the cohort, which makes the present study population unique and appropriate for investigating the impact of DASH and MED diet adherence and related inflammatory marker CRP. Over the last two decades, Food Frequency Questionnaires (FFQ) become a widely accepted method to assess the usual intake and has been used widely in epidemiologic studies [98].

However, several limitations need to be acknowledged. Cache County Memory Study does not have a collection of blood for inflammatory markers at the Wave 1 baseline examination that would allow a prospective study of CRP levels and subsequent cognitive outcomes. We also used a single inflammatory marker, CRP, to determine the plasma level of inflammatory biomarkers, but due the complexity of systemic inflammation [94], examining multiple inflammatory biomarkers would help to strengthen our results.

In conclusion, the results of the present study confirmed that MED and DASH are associated with lower risk of elevated systemic inflammation as indicated by CRP levels. This association appears to be modified by BMI, with overweight and the obese person having a stronger association than normal weight person. These results observed after controlling for gender, age, educational level, drinking and smoking habits, diabetes, stroke, heart attack, multivitamin and minerals use, and APOE genotype. MED is a formula for healthy day-to-day eating over a period, and people have eaten it for centuries, and adherents live longer with lower rates of heart disease,

cancer, and dementia. DASH diet was demonstrated to lower blood pressure. DASH also has been found to improve health by lowering cholesterol and preventing diabetes and increasing life expectancy. Thus, there is good scientific support recommending MED and DASH diets because both of these diets serve as anti-inflammatory diets and offer health benefits that can promote substantial protection against many conditions influenced by inflammatory biomarkers.

Table 3.1: Food groups and nutrient scoring criteria for Mediterranean Diet (MED) score and Dietary Approach to Stop Hypertension (DASH) score; Cache County Memory Study (n =1713)

Food Group	Food Items	Scoring Criteria	Median (25th, 75th percentiles)	DASH Diet Components	MED Components
Fruits (serv/d)	All fruits and 100% fruit juices	Positive	2.8 (2.0, 3.8)	Yes	Yes
Vegetables (serv/d)	All vegetables except potatoes and legumes	Positive	2.7 (1.9, 3.8)	Yes	Yes
All meat (serv/d)	Beef, pork, lamb, chicken, turkey, liver, salami, bologna, hot dogs, bacon, sausage, other processed meats	Negative	0.69 (0.47, 0.98)	No	Yes
Red and processed meats (serv/d)	Beef, pork, lamb, liver, salami, bologna, hot dogs, bacon, sausage, other processed meats	Inverse	0.63 (0.38, 1.1)	Yes	No
Whole grains (serv/d)	Dark bread or pita, whole-grain cold breakfast cereals, cooked cereal, oatmeal, popcorn, other grains (e.g. bulgur, kasha, couscous)	Positive	1.5 (1.0, 2.5)	Yes	No
Nuts (serv/d)	Peanuts, peanut butter, other nuts	Positive[2]	0.35 (0.14, 0.86)	Yes	No
Legumes (serv/d)	Dried beans, peas, lentils, tofu, soybeans, green beans	Positive[2]	0.34 (0.22, 0.57)	Yes	Yes
Full-fat dairy (serv/d)	Whole milk, chocolate milk, ice cream, cheddar and other hard cheese	Negative	1.5 (0.89, 2.4)	No	Yes
Low-fat dairy (serv/d)	Skim or low-fat milk, yogurt, cottage or ricotta cheese	Positive	1.3 (0.93, 2.6)	Yes	No
Sweetened beverages (serv/d)	Sweetened beverages, including soda pop, punch, and other sweetened beverages	Inverse	0.14 (0.00, 0.500)	Yes	No
Fish (serv/d)	Dark meat fish, other white meat fish	Positive	0.16 (0.09, 0.27)	No	Yes
MUFA/SUFA ratio	Ratio of total monounsaturated fatty acids/total saturated fatty acids	Positive	0.11 (0.10, 0.12)	No	Yes
Sodium (mg/d)	Sum of sodium content of all foods	Inverse	2653 (2033, 3416)	Yes	No

[1]Positive scoring in Wave 3 of the CCMS: participant consuming the lowest amount received a rank score of 1, participant with highest amount received rank score of 1713; negative scoring: participant consuming the lowest amount received a rank score of 1713, participant with the highest amount received rank score of 1.

[2] Nuts and legumes combined for DASH-style diet pattern score.

Table 3.2: Participant characteristics by quintiles of the 8-component DASH diet score in the Cache County Study on Memory.

| Characteristic | Quintiles and ranges of DASH scores | | | | | p-value[1] |
	Quintile 1 (n= 365) 1602- 5693	Quintile 2 (n= 365) 5694- 6815	Quintile 3 (n= 366) 6816- 7778	Quintile 4 (n= 364) 7779- 8927	Quintile 5 (n= 366) 8928- 14,049	
Mediterranean scores [2]	5993± 1619	6675± 1577	7325± 1544	7675± 1536	8866± 1697	<0.001
Mean CRP (mg/L) [2]	4.9± 7.3	4.7± 6.5	4.3± 6.0	4.1± 6.0	4.0± 6.6	0.033
Gender (%) - Male - Female	27.1 15.1	22.4 18.4	16.2 22.2	18.1 21.0	16.2 23.3	<0.001
Age (y) [2]	73.1± 5.5	72.5± 5.7	72.5± 5.1	72.5± 5.2	73.4± 5.4	0.157
Mean BMI (kg/m) [2]	25.9± 4.6	27.1± 4.7	26.3± 3.9	26.5± 4.2	25.6± 4.0	<0.001
More than high school education (%)	17.8	20.5	17.9	15.3	14.7	<0.001
MVM use (%)	22.7	20.9	18.7	19.5	18.2	0.004
Ever smoke (%)[3]	17.4	20.1	20.6	20.1	21.8	<0.001
Ever alcohol (%)[3]	18.5	20.0	20.1	20.1	20.8	0.018
At least one APOE e4 allele (%)	18.6	20.7	18.1	19.1	23.1	0.434
Diagnosed with diabetes (%)	18.2	24.2	16.2	19.9	21.5	0.181
Diagnosed with stroke (%)	26.6	21.6	18.7	15.1	18.1	0.210
Diagnosed with heart attack (%)	22.7	22.7	16.4	22.3	16.0	0.104
Dietary intake[2]: Energy (kcal)	2023± 692	1877± 664	1788± 634	1853± 591	2005± 570	<0.001
Fat (g)[4]	79.4± 11.0	75.8± 12.8	73.0± 11	69.1± 10.9	66.0± 12.6	<0.001
Carbohydrate (g)[4]	81.8± 19.7	83.9± 19.2	83.2± 18.5	86.9± 16.0	85.1± 17.6	0.014
Protein (g)[4]	74.9± 14.9	75.3± 13.7	76.1± 13.4	74.8± 12.5	74.8± 13.3	0.340
Saturated fats (g)[4]	27± 5.8	25.1± 5.6	24.1±5.0	22.6± 4.8	20.7± 5.3	<0.001
Monounsaturated fats (g)[4]	25.9± 5.6	25.7± 6.7	25± 5.5	23.5± 5.2	23.3± 5.8	<0.001
Polyunsaturated (g)[4]	11.2± 3.4	11.5± 3.6	11.2± 3.2	11± 3.4	11.5± 3.6	0.321
Ratio MUFAs to SFSAs	0.10± 0.18	0.11± 0.02	0.11± 0.02	0.11±0.02	0.12± 0.02	<0.001
Omega-3 fatty acids(g)[4]	1.1± 0.44	1.0±0.43	1.1± 0.42	1.0± 0.44	1.1± 0.59	0.256

Omega-6 fatty acids (g)[4]	9.2± 3.2	9.5± 3.4	9.3± 2.9	9.0± 3.1	9.6± 3.4	0.332
Cholesterol (mg)[4]	333± 194	294± 141	276± 97	255± 947	236± 123	<0.001
Fiber (g)[4]	15.7± 4.1	17± 4.4	19.8± 4.3	21.5± 4.2	24.8± 6.8	<0.001
Vitamin C (mg)[4]	106± 49.8	117± 48.8	134± 47	144± 52.4	167± 62.6	<0.001
Folate (µg)[4]	364± 91	397± 92	414± 86	451± 109	471± 109	<0.001
Vitamin B-6 (mg)[4]	1.6± 0.45	1.8± 0.41	1.8± 0.40	2.0± 0.45	2.0± 0.47	<0.001
Vitamin B-12 (µg)[4]	5.1± 2.3	5.6± 2.9	5.4± 2.2	6.0±5.3	5.1± 2.2	0.003
Sodium (mg)[4]	3019± 456	2901±532	2774± 509	3050±472	2523± 469	0.023
Calcium (mg)[4]	813± 261	927± 305	968± 263	1055± 298	1057± 313	<0.001
Potassium (mg)[4]	2637± 508	2902± 434	3095± 448	3287± 456	3588± 538	<0.001
Magnesium (mg)[4]	253± 45	287± 43	304± 36	326± 39	357± 48	<0.001
Zinc (mg)[4]	10± 2.7	10.6±2.9	10.7± 2.7	11.2± 3.1	11.1± 2.9	<0.001

[1] p-values were obtained by using the Chi-square test for categorical variables and Analysis of Variance (ANOVA) for continuous variables. DASH, Dietary Approaches to Stop Hypertension; MVM, multivitamin-mineral supplement; BMI, Body Mass Index, CRP, C-reactive protein.
[2] Means ± standard deviation (SD).
[3] An ever smoker was defined as a subject who reported ever regularly smoking; an ever drinker was defined as a subject who reported ever regularly drinking alcohol.
[4] Energy-adjusted nutrient intakes per day.

Table 3.3 Participant characteristics by quintiles of the 8-component Mediterranean diet score in the Cache County Study on Memory.

Characteristic	Quintiles and ranges of MED scores					p-value[1]
	Quintile 1 (n= 365) 2033- 5684	Quintile 2 (n= 365) 5685-6795	Quintile 3 (n= 366) 6796- 7818	Quintile 4 (n= 364) 7819- 8856	Quintile 5 (n= 366) 8857- 13,525	
DASH score[2]	6400± 1920	6939± 1668	7261± 1668	7638± 1771	8175± 1767	<0.001
Mean CRP (mg/L)[2]	4.8± 7.5	4.5± 5.6	4.3± 6.7	4.4± 5.8	3.9± 6.7	0.069
Gender % - Male - Female	187 (27.1) 152 (14.9)	140 (20.3) 198 (20.9)	125 (18.1) 214 (20.9)	121 (17.5) 225 (22.0)	118 (17.1) 233 (22.8)	<0.001
Age (y)[2]	76.5± 5.4	72.6± 5.3	73.1± 5.7	73.0± 5.6	72.8± 5.1	0.606
Mean BMI (kg/m)[2]	26.5± 4.4	26.5± 3.9	26.6± 4.3	26.4± 4.3	26.0± 4.1	0.178
More than high school education (%)	18.6	17.9	19.0	20.1	24.3	0.004
MVM use (%)	21.7	19.6	19.9	19.1	19.8	0.239
Ever smoke (%)[3]	18.0	20.9	19.4	20.1	21.5	<0.001
Ever alcohol (%)[3]	18.8	20.3	20.2	20.3	20.4	<0.001
At least one APOE e4 allele (%)	19.6	20.2	20.8	20.0	19.4	0.235
Diagnosed with diabetes (%)	19.9	20.4	20.0	20.5	20.0	0.787
Diagnosed with stroke (%)	20.2	19.8	19.6	20.3	20.1	0.486
Diagnosed with heart attack (%)	19.5	15.2	18.0	29.3	18.0	0.002
Dietary intake[3] Energy (kcal)	2030± 670	1903± 624	1850± 636	1858± 624	1911± 620	0.002
Fat (g)[4]	80± 11.8	75± 10.9	72± 11.3	70± 11.7	64± 11.6	<0.001
Carbohydrate (g)[4]	235± 29	247± 27	251± 27	260± 28	273± 29	<0.001
Protein (g)[4]	74.3± 14.4	75.5± 13.3	76.4± 13.9	75.5± 13.5	76.1± 12.8	0.402
Saturated fats (g)[4]	29± 5.5	25± 4.4	23± 4.6	22± 4.0	18± 4.3	<0.001
Monounsaturated fats (g)[4]	27± 6.1	25± 5.8	24± 5.4	23± 5.6	22± 5.3	<0.001
Polyunsaturated (g)[4]	10± 3.3	10± 3.7	11± 3.4	11± 3.3	12± 3.4	<0.001
Ratio MUFAs to SFSAs	0.1± 0.01	0.1± 0.01	0.11± 0.01	0.12± 0.02	0.13± 0.02	<0.001
Omega-3 fatty acids(g)[4]	0.95± 0.38	0.99± 0.43	1.1± 0.42	1.1± 0.43	1.3± 0.58	<0.001
Omega-6 fatty acids (g)[4]	8.4± 3.1	9.1± 3.5	9.4± 3.1	9.7± 3.1	10± 3.05	<0.001
Cholesterol (mg)[4]	311± 160	297± 128	289± 165	266± 113	228± 97	<0.001
Fiber (g)[4]	15± 3.7	18± 3.6	19± 4.1	21± 3.9	25± 6.8	<0.001

Vitamin C (mg)[4]	100± 47.9	122± 49.3	128± 46.8	147± 48.4	171± 61.6	<0.001
Folate (µg)[4]	349± 88	395± 89.7	416± 87.2	445± 91.9	494± 108	<0.001
Vitamin B-6 (mg)[4]	1.6± 0.44	1.8± 0.41	1.8± 0.44	1.9± 0.41	2.1± 0.45	<0.001
Vitamin B-12 (µg)[4]	5.7± 2.8	5.5± 2.2	5.7± 5.3	5.3± 2.3	4.9± 2.3	<0.021
Sodium (mg)[4]	2694± 569	2830± 506	2860± 533	2827± 520	3045± 471	0.421
Calcium (mg)[4]	1046± 349	1013± 297	951± 298	913± 278	902± 257	<0.001
Potassium (mg)[4]	2780± 530	3000± 507	3052±530	3235± 499	3466± 582	<0.001
Magnesium (mg)[4]	271± 50	293± 43	299± 47	319± 46	347± 56	<0.001
Zinc (mg)[4]	10.4± 2.7	10.7± 2.6	10.8± 3.2	10.8± 2.8	11.1± 3.03	0.135

[1] p-values were obtained by using the Chi-square test for categorical variables and Analysis of Variance (ANOVA) for continuous variables. DASH, Dietary Approaches to Stop Hypertension; MVM, multivitamin-mineral supplement; BMI, Body Mass Index, CRP, C-reactive protein.

[2] Means ± standard deviation (SD).

[3] An ever smoker was defined as a subject who reported ever regularly smoking; an ever drinker was defined as a subject who reported ever regularly drinking alcohol.

[4] Energy-adjusted nutrient intakes per day.

Table 3.4: Odds ratio of clinically relevant elevation of CRP (> 3.00 mg/L) by quintile of the DASH diet score, Mediterranean diet score, and their respective food items in the Cache County Memory (n = 1713).

	Quintile of accordance score or food group					p-linear trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
DASH and components (multivariable adjusted)[1]						
DASH	1.00 [reference]	0.98 (0.70- 1.3)	0.96 (0.68- 1.3)	0.78 (0.55- 1.0)	0.74 (0.53- 1.05)	0.036
Whole grain	1.00 [reference]	1.10 (0.82- 1.5)	0.89 (0.64- 1.2)	0.74 (0.53- 1.0)	1.00 (0.74- 1.4)	0.348
Nuts and legumes	1.00 [reference]	0.99 (0.71- 1.3)	0.86 (0.62- 1.2)	0.84 (0.60- 1.1)	0.72 (0.51- 1.0)	0.039
Fruits	1.00 [reference]	1.20 (0.88- 1.7)	0.98 (0.70- 1.3)	1.00 (0.71- 1.4)	0.89 (0.63- 1.2)	0.249
Vegetables	1.00 [reference]	0.81 (0.58- 1.2)	0.76 (0.55- 1.0)	0.70 (0.50- .97)	0.84 (0.60- 1.1)	0.197
Red and processed meat	1.00 [reference]	1.20 (0.86- 1.6)	1.00 (0.72- 1.4)	1.30 (0.98- 1.9)	1.20 (0.89- 1.7)	0.136
Low-fat dairy	1.00 [reference]	1.00 (0.75- 1.4)	0.88 (0.63- 1.2)	1.20 (0.89- 1.6)	1.00 (0.77- 1.5)	0.366
Sweetened beverages	1.00 [reference]	0.66 (0.48- 0.9)	0.70 (0.50- 97)	0.78 (0.56- 1.0)	0.89 (0.64- 1.2)	0.801
Sodium	1.00 [reference]	1.00 (0.74- 1.4)	1.20 (0.89- 1.4)	1.10 (0.79- 1.5)	1.10 (0.85- 1.6)	0.284
Mediterranean and components (multivariable adjusted)[1]						
MED	1.00 [reference]	1.00 (0.72- 1.4)	0.73 (0.52- 1.0)	1.00 (0.74- 1.4)	0.73 (0.52- 1.0)	0.131
All grains	1.00 [reference]	0.94 (0.68- 1.3)	0.81 (0.58- 1.1)	1.00 (0.76- 1.4)	0.91 (0.65- 1.2)	0.864
Legumes	1.00 [reference]	0.96 (0.69- 1.3)	0.74 (0.53- 1.0)	0.78 (0.56- 1.1)	0.75 (0.54- 1.0)	0.048
Fruits	1.00 [reference]	1.30 (0.98- 1.9)	0.91 (0.65- 1.2)	1.00 (0.76- 1.5)	0.88 (0.63- 1.2)	0.204
Vegetables	1.00 [reference]	0.81 (0.58- 1.1)	0.80 (0.57- 1.1)	0.77 (0.55- 1.0)	0.86 (0.61- 1.2)	0.368
Meat and meat products	1.00 [reference]	1.00 (0.73- 1.4)	1.00 (0.72- 1.3)	0.97 (0.70- 1.3)	0.93 (0.67- 1.3)	0.651
Full fat dairy	1.00 [reference]	0.94 (0.67- 1.3)	1.10 (0.81- 1.6)	1.40 (0.99- 1.9)	1.30 (0.99- 1.9)	0.006
Fish	1.00 [reference]	0.72 (0.52- 1.0)	0.88 (0.63- 1.2)	0.84 (0.60- 1.1)	1.00 (0.75- 1.4)	0.488
Ratio of MUFAs to SFA	1.00 [reference]	0.70 (0.50- 0.9)	0.94 (0.67- 1.3)	0.91 (0.65- 1.2)	0.55 (0.54- 1.0)	0.514

[1]The multivariable model included the following covariates: age, sex, BMI, education, APOE, history of drinking and smoking, and history of diabetes, heart attack, and stroke.

Table 3.5: Odds ratio of clinically relevant elevation of CRP (> 3.00 mg/L) by quintile of the DASH diet score, Mediterranean diet score, and their respective food items in the Cache County Memory (n= 914): overweight and obese participants (BMI ≥25) only.

	Quintile of accordance score or food group					p-linear trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
DASH and components (multivariable adjusted)[2]						
DASH	1.00 [reference]	1.05 (0.68- 1.6)	0.81 (0.68-1.2)	0.76 (0.49- 1.2)	0.65 (0.41-1.0)	0.027
Whole grain	1.00 [reference]	1.00 (0.772- 1.4)	0.84 (0.61-1.1)	0.72 (0.52- 1.0)	0.99 (0.72- 1.3)	0.383
Nuts and legumes	1.00 [reference]	0.88 (0.57- 1.3)	0.74 (0.48-1.1)	0.55 (0.35- .88)	0.60 (0.38 - .94)	0.004
Fruits	1.00 [reference]	1.20 (0.80- 1.9)	0.94 (0.61-1.4)	0.79 (0.51- 1.2)	0.77 (0.49- 1.2)	0.067
Vegetables	1.00 [reference]	0.75 (0.48- 1.1)	0.61 (0.39-.97)	0.66 (0.42- 1.0)	0.68 (0.43- 1.0)	0.101
Red and processed meat	1.00 [reference]	1.40 (0.93- 2.3)	1.10 (0.73- 1.8)	1.50 (0.95- 2.4)	1.30 (0.84- 2.1)	0.329
Low-fat dairy	1.00 [reference]	0.96 (0.62- 1.5)	0.75 (0.47-1.2)	1.20 (0.81- 2.0)	0.98 (0.62- 1.5)	0.070
Sweetened beverages	1.00 [reference]	0.65 (0.42- 1.0)	0.19 (0.50-1.2)	0.61 (0.61- 1.4)	0.70 (0.46- 1.0)	0.505
Sodium	1.00 [reference]	1.10 (0.71- 1.8)	1.20 (0.76- 1.9)	1.30 (0.86- 2.2)	1.20 (0.75- 1.9)	0.306
Mediterranean and components (multivariable adjusted)[1]						
Mediterranean	1.00 [reference]	0.78 (0.50- 1.2)	0.62 (0.40-.97)	0.73 (0.47- 1.1)	0.55 (0.35-0.89)	0.018
All grains	1.00 [reference]	0.89 (0.57- 1.3)	0.72 (0.46 1.1)	1.00 (0.66- 1.5)	0.78 (0.50- 1.1)	0.488
Legumes	1.00 [reference]	0.87 (0.56- 1.3)	0.75 (0.48-1.1)	0.74 (0.47- 1.1)	0.59 (0.38-0.93)	0.021
Fruits	1.00 [reference]	1.30 (0.86- 2.0)	0.85 (0.55-1.3)	0.89 (0.57- 1.4)	0.71 (0.45- 1.1)	0.049
Vegetables	1.00 [reference]	0.74 (0.48- 1.1)	0.65 (0.42-1.0)	0.74 (0.46- 1.1)	0.66 (0.42- 1.0)	0.131
Meat and meat products	1.00 [reference]	0.86 (0.54- 1.3)	0.81 (0.52-1.2)	0.79 (0.50- 1.2)	0.86 (0.55- 1.3)	0.509
Full fat dairy	1.00 [reference]	0.94 (0.60- 1.4)	0.97 (0.61-1.5)	1.30 (0.85- 2.1)	1.40 (0.96- 2.3)	0.020
Fish	1.00 [reference]	0.83 (0.54- 1.3)	0.73 (0.46-1.1)	0.80 (0.52- 1.2)	0.90 (0.58- 1.4)	0.677
Ratio of MUFAs to SFA	1.00 [reference]	0.73 (0.47- 1.1)	0.76 (0.49-1.1)	0.88 (0.56- 1.3)	0.63 (0.40- 1.0)	0.172

[1]The multivariable model included the following covariates: age, sex, education, BMI, APOE, history of drinking and smoking, and history of diabetes, heart attack, and stroke.

Table 3.6: Odds ratio of clinically relevant elevation of CRP (> 3.00 mg/L) by quintile of the DASH diet score, Mediterranean diet score, and their respective food items in the Cache County Memory (n = 914): non-overweight and non-obese participants (BMI <25) only.

	Quintile of accordance score or food group					p-linear trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
DASH and components (multivariable adjusted)[1]						
DASH	1.00 [reference]	0.886 (0.51- 1.5)	1.10 (0.71-1.9)	0.808 (0.47- 1.3)	0.856 (0.52-1.4)	0.46
Whole grain	1.00 [reference]	1.20 (0.75- 2.0)	0.778 (0.46-1.3)	0.776 (0.46- 1.3)	1.05 (0.64- 1.7)	0.54
Nuts and legumes	1.00 [reference]	1.16 (0.68- 1.9)	1.08 (0.65-1.8)	1.30 (0.84- 2.2)	1.30 (0.57 – 1.6)	0.83
Fruits	1.00 [reference]	1.20 (0.76- 2.1)	1.05 (0.62-1.8)	1.30 (0.82- 2.3)	1.05 (0.63- 1.7)	0.81
Vegetables	1.00 [reference]	0.718 (0.43- 1.2)	0.925 (0.56- 1.5)	0.702 (0.41- 1.1)	0.990 (0.60- 1.6)	0.95
Red and processed meat	1.00 [reference]	0.995 (0.60- 1.6)	0.844 (0.50- 1.3)	1.30 (0.82- 2.1)	1.20 (0.74- 1.9)	0.24
Low-fat dairy	1.00 [reference]	1.22 (0.73- 2.02)	1.07 (0.65-1.7)	1.20 (0.76- 2.0)	1.27 (0.76- 2.1)	0.37
Sweetened beverages	1.00 [reference]	0.690 (0.42- 1.1)	0.58 (0.35-.96)	0.588 (0.35- 0.98)	1.20 (0.73- 1.9)	0.85
Sodium	1.00 [reference]	0.916 (0.55- 1.5)	1.30 (0.85- 2.1)	0.767 (0.46- 1.2)	1.20 (0.74- 1.9)	0.71
Mediterranean and components (multivariable adjusted)[1]						
Mediterranean	1.00 [reference]	1.30 (0.80- 2.3)	0.878 (0.51-1.4)	1.40 (0.90- 2.4)	0.980 (0.58-1.6)	0.91
All grains	1.00 [reference]	0.968 (0.58- 1.6)	0.886 (0.52 1.4)	1.00 (0.62- 1.8)	1.07 (0.61- 1.7)	0.67
Legumes	1.00 [reference]	1.20 (0.72- 2.01)	0.681 (0.40-1.1)	0.832 (0.49- 1.3)	1.00 (0.60- 1.6)	0.52
Fruits	1.00 [reference]	1.4 (0.85- 2.4)	0.985 (0.58-1.6)	1.36 (0.808- 2.3)	1.10 (0.66- 1.8)	0.82
Vegetables	1.00 [reference]	0.866 (0.52- 1.4)	1.05 (0.63- 1.7)	0.806 (0.48- 1.3)	1.12 (0.68- 1.8)	0.78
Meat and meat products	1.00 [reference]	1.26 (0.78- 2.0)	1.20 (0.77- 2.0)	1.20 (0.77- 2.0)	1.02 (0.60- 1.7)	0.86
Full fat dairy	1.00 [reference]	0.928 (0.55- 1.5)	1.44 (0.67-2.3)	1.50 (0.94- 2.6)	1.50 (0.80- 2.2)	0.05
Fish	1.00 [reference]	0.601 (0.35- 1.0)	1.09 (0.66-1.8)	0.915 (0.55- 1.5)	1.26 (0.77- 2.0)	0.13
Ratio of MUFAs to SFA	1.00 [reference]	0.689 (0.40- 1.1)	1.20 (0.77- 2.0)	0.976 (0.58- 1.6)	0.95 (0.58- 1.5)	0..69

[1]The multivariable model included the following covariates: age, sex, education, BMI, APOE, history of drinking and smoking, and history of diabetes, heart attack, and stroke.

Table 3.7: Spearman rank order correlation coefficients of the CRP and Mediterranean Diet (MED) and the Dietary Approaches to Stop Hypertension (DASH) scores with nutritional factors; Cache County Memory Study.

Nutrients	Correlation with MED (p-values)	Correlation with DASH (p-values)	Correlation with CRP (p-values)
Total calorie intake	-0.071** (0.003)	0.000 (0.992)	-0.015 (0.516)
Protein	0.026 (0.278)	0.014 (0.591)	0.049* (0.049)
Carbohydrate	0.421** (0.010)	0.063** (0.018)	-0.026 (0.298)
Fiber	0.639** (<0.001)	0.589** (<0.001)	-0.063* (0.010**)
Total sugar	0.076** (0.004)	0.134** (<0.001)	0.015 (0.556)
Monosaccharide	0.409** (<0.001)	0.488** (<0.001)	-0.030 (0.220)
Disaccharide	0.272** (<0.001)	0.248** (<0.001)	0.006 (0.821)
Total fats	-0.424** (<0.001)	-0.397** (<0.001)	-0.004 (0.870)
Saturated fats	-0.612** (<0.001)	-0.397** (<0.001)	0.014 (0.579)
Monounsaturated fats	-0.279** (<0.001)	-0.182** (<0.001)	-0.015 (0.553)
Polyunsaturated	0.193** (<0.001)	-0.003 (0.791)	0.061* (0.013)
Cholesterol	-0.228** (<0.001)	-0.260** (<0.001)	0.073** (0.003)
Thiamine (B1)	0.333** (<0.001)	0.292** (<0.001)	-0.018 (0.473)
Riboflavin (B2)	-0.104** (<0.001)	0.241** (<0.001)	0.018 (0.458)
Niacin (B3)	0.263** (<0.001)	0.044 (0.132)	-0.026 (0.300)
Pyridoxine (B6)	0.363** (<0.001)	0.324** (<0.001)	-0.015 (0.381)
Cobalamin (B12)	-0.123** (<0.001)	0.031 (0.218)	-0.022 (0.226)
Ascorbic acid ©	0.435** (<0.001)	0.397** (<0.001)	0.030 (0.681)
Folate	0.483** (<0.001)	0.387** (<0.001)	-0.035 (0.151)
Pantothenic acid	0.113** (<0.001)	0.324** (<0.001)	0.026 (0.295)
Calcium	-0.179** (<0.001)	0.318** (<0.001)	-0.011 (0.464)
Copper	0.486** (<0.001)	0.409** (<0.001)	-0.020 (0.418)
Iron	0.355** (<0.001)	0.208** (<0.001)	-0.033 (0.177)
Magnesium	0.482** (<0.001)	0.699** (<0.001)	-0.026 (0.293)
Manganese	0.561** (<0.001)	0.576** (<0.001)	-0.048 (0.051)
Phosphorus	-0.029 (0.266)	0.355** (<0.001)	0.046 (0.062)
Potassium	0.413** (<0.001)	0.598** (<0.001)	0.009 (0.713)
Selenium	0.189** (<0.001)	0.020(0.458)	0.046 (0.063)
Sodium	0.028 (0.282)	-0.338** (<0.001)	0.018 (0.459)
Zinc	0.052* (0.048)	0.139** (<0.001)	0.010 (0.671)
Omega 3	0.268** (<0.001)	0.032 (0.462)	-0.048 (0.054)
Omega 6	0.192** (<0.001)	0.008 (0.757)	-0.064** (0.010)
Omega6:omega3	-0.126** (<0.001)	-0.040 (0.095)	0.046 (0.395)
Alcohol	0.096** (<0.001)	0.018(0.498)	0.004 (0.861)
Caffeine	-0.107** (<0.001)	-0.172** (<0.001)	0.046 (0.063)

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
Note: Nutrients in which correlations are different between DASH, the Mediterranean Diet (MED), and C-reactive protein (CRP).

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CHAPTER 4

ERYTHROCYTE MEMBRANE FATTY ACID COMPOSITION AND SYSTEMIC

INFLAMMATION IN THE CACHE COUNTY MEMORY STUDY

Abstract

Objective: To evaluate whether erythrocyte membrane fatty acids composition (EMFAs) are associated with elevated plasma inflammatory C- reactive protein (CRP) levels.

Design: 1844 men and women aged ≥65 years and older at the baseline participated in the Cache County Memory Study (CCMS) and who resident of Cache County, Utah. Fatty acid (FA) composition was measured in serum fatty acid methyl esters and were examined in relation to high-sensitivity C-reactive protein. Multivariable logistic regression models were used to estimate the risk of CRP elevation (> 3.0mg/L) by increasing tertiles of EMFA, with control for potential confounding factors.

Results: Risk of elevated CRP was increased in tertile 3 vs. tertile 1 of palmitoleic acid, and nervonic acids, both monounsaturated fatty acids (MUFA), (aOR=1.7 [95%CI 1.3-2.2], aOR=1.3 [95%CI 1.0-1.6], respectively), and dihomo-y-linolenic acid (DGLA), doco-sapentaenoic acid (DPA-6), docosahexaenoic acid (DHA), all polyunsaturated fatty acids (PUFA), (aOR=1.5 [95%CI 1.2-1.9], aOR=1.3 [95%CI 1.0- 1.6], aOR=1.2 [95%CI 1.0- 1.6]), respectively. Conversely, risk of CRP elevation was reduced in tertile 3 vs. tertile 1 of margaric acid, stearic acid, and arachidic acid, all saturated fatty acids (SFA), (aOR=0.67 [95%CI 0.53- 0.89], aOR=0.78 [95%CI 0.60- 0.99], and aOR=0.69 [95%CI 0.53- 0.88]), respectively. These associations appeared stronger among women compared to men.

Conclusions: Several erythrocyte membrane fatty acids were associated with plasma CRP level, a marker of systemic inflammation. Unexpectedly, all associations with reduced CRP level were among SFAs and all associations with increased CRP level were among MUFAs and PUFAs.

Introduction

Alzheimer's disease (AD) is a result of a neurodegenerative disease that affects memory and thinking skills [1]. The prevalence of AD increases with age [1] and the number of people with AD are growing due to physical inactivity, social isolation, cardiovascular disease, diabetes, and diet [2]. Neuro- and vascular inflammation may participate in the pathogenesis of AD [3] and markers of systemic inflammation have been associated with AD [4, 5].

The underlying cause of systemic inflammation is unclear, but one contributing factor may be dietary fatty acids (FAs) [6, 7]. Serum and plasma fatty acid composition have been used as a biomarker of dietary fat quality [8-10]. FAs may contribute to pro-inflammatory and anti-inflammatory mechanisms [11]. This concept noticeably changes the understanding of the role of high intake of FAs in the western diet and inflammation [12].

FA composition has been studied extensively in experimental, observational, and human health studies [13-17]. FA composition of plasma also affects endogenous elongation and desaturation catalyzed by several enzymes [18]. Omega-3 fatty acids (n-3) and omega-6 FAs (n-6) make up a families of polyunsaturated fatty (PUFA) acids that are essential in small quantities for health benefits because humans do not have the mechanisms to synthesize them [19, 20]. While omega- 3 FAs come from fish oils and flaxseed, canola, soy, perilla, and walnut oils [21], omega-6 FAs are mainly found in vegetable oils including palm, soybean, rapeseed, and sunflower [22].

Docosahexaenoic acid (DHA), a long chain omega-3 FA, is one of the major FAs in the brain and has been hypothesized as anti-inflammatory. Animal and human trials studies have shown that DHA is associated with decreased CRP concentration [23-25] and other inflammatory biomarkers [26-36]. Concomitantly, omega-6 fatty acid consumption is still a controversial issue, because human observational and experimental studies suggest that n-6 fatty acids have both pro-inflammatory [37, 38] and anti-inflammatory [39, 40] effects.

Given the increased interest in research in this area, FA composition of the diet among elderly will be the focus of much discussion and debate. In the present study, we examined the associations between erythrocyte membrane fatty acid composition and systemic inflammation levels as indicated by level of inflammatory CRP levels, using the data from the Cache County Memory Study (CCMS), also taking several potential confounding variables into account.

Materials and Methods

Study participants

The Cache County Memory Study (CCMS) is a prospective cohort study with participants aged ≥65 years and older at the baseline who were a resident of Cache County, Utah. This population is largely non-Hispanic White, and the genetic makeup is mostly from Northern European ancestry. The baseline interview included information about demographic characteristics, health history, and family history of dementia, use of medications, alcohol, tobacco, other lifestyle factors, and extensive cognitive testing. Reassessments of participants were completed in subsequent years with sample size at the Wave 2 examination in 1998-1999, of 3,411; Wave 3 in 2002-2003 with 2,344; and Wave 4 in 2005-2006 with 1,137. In Wave 3, a non-fasting venous blood sample, diet, and cognitive data were collected from 2252 participants.

Exclusions included 108 participants who did not complete a dietary assessment and 62 who did not provide a blood sample. Moreover, 203 participants were eliminated from the analyses because the percent contribution of fatty acids in their erythrocyte membranes could not be determined, and an additional 7 were excluded because they provided implausible dietary intakes of <500 or >5000 kcal per day. The final sample size was 1987. Participants provided signed consent to participate. The institutional review boards of each collaborating site at Utah State University, Duke University Medical Center, and The Johns Hopkins University approved the protocol of the study. Details of the study protocols have been previously published [41].

Fatty acid assessment

Blood samples were drawn from the arm and were collected during the third examination Wave in 2002. Erythrocytes (red blood cells, RBCs) were analyzed by using the gas chromatography (GC) method. RBCs mixed with deionized water to direct transesterification after the sample was thawed, and then centrifuged at 10,000 x g for 5 minutes [42]. The resulting product was mixed with 1.9 ml of a solution containing 1.7 ml methanol, 100 ul acetyl chloride, and 100 ul internal standards. The tubes were capped and then heated to 100 ul for 60 minutes. After cooling the tubes, 0.75 ml of hexane was added and the tubes were vortexed for 30 seconds. A Shimadzu GC-2010 with a flame ionization detector was used to analyze fatty acid methyl esters [43]. The amount of analyzed EMFA was expressed as a percentage. The 23 EMFAs assayed are listed in Table 4.2.

CRP assessment

Non-fasting blood samples were collected and assayed for high- sensitivity C-reactive protein (hs-CRP) from 2185 participants in Wave 3 at McKay Dee Laboratory Hospital, Ogden, UT. A Dade Behring BNII (BN for Behring

Nephelometer) was used for measurement, considered as a gold standard for these tests in the laboratory industry [44]. Many large reference studies refer to the Dade BNII assay that uses particle enhanced immunonephelometry. Dade was one of the first vendors to receive FDA approval for cardiac marker claims for their sensitive CRP assay [45]. The method uses polystyrene particles coated with mouse monoclonal antibodies to CRP that are agglutinated when mixed with samples containing CRP [46]. The intensity of the scattered light in the nephelometer depends on the CRP content of the sample and, therefore, the CRP concentration. Typically, expected values for healthy individuals are found to be < 3.0 mg/L, or < 0.3 mg/dL [45]. The actually measuring range is determined by the lower limit of the reference curve and depends on the concentration of the standard used. The typical limit of detection for the method was 0.175 mg/L or 0.0175 mg/dL. The upper level of detection was typically 1150 mg/L or 150 mg/dL. We clinically defined elevated CRP as values >3.0 mg/L [45].

Statistical Analyses

Baseline characteristics were analyzed and presented by CRP levels. We reported selected sociodemographic variables, medical, and behavior characteristic of the participants. Percent composition of EMFAs was categorized into tertiles of the cohort's distribution of each EMFA.

Analysis of Variance (ANOVA) was used to test whether there were statistically significant differences between the means of EMFAs in elevated vs. normal CRP levels. Potential confounding variables including body mass index (BMI) (kg/m2, continuous), smoking (never, former, current), age in years (65-74, 75-84, 85+), education levels (less than high school, more than high school), and gender (male, female) were evaluated. We estimated the odds ratio (ORs) and 95% confident

intervals (CIs) for CRP elevation by increasing tertiles of EMFA levels using logistic regression models while controlling for potential covariates. Gender was found in previous studies to be associated with habitual intake of fatty acids [47, 48] and it also appeared to differ the ability to synthesize fatty acids [49, 50], thus models for adjusted odds ratios included gender as a covariate and analyses were stratified by gender to examine effect modification by gender. Participants with no dementia (n = 154) were excluded from all analysis. Statistical analysis was performed using software package SPSS version 22. Reported p-values are two-sided, and the type I error rate for statistical significance was 0.05.

Results

Demographic characteristics are presented in Table 4.1. The average age was 73 ± 5.5 years. Elevated CRP levels were found more often in women, the less educated, current smokers, and those with a history of stroke and was associated with higher BMI. Apolipoprotein (APOE) ε4 allele was associated with lower CRP levels.

Table 4.2 shows the relative percentage of the measured 23 EMFAs. Saturated fatty acids (SFAs) accounted for 47% of all identified fatty acids, trans-fat (TFA) accounted 0.43%, and monounsaturated fatty acid (MUFA) accounted 8.3%, and PUFAs accounted for 16.5%; the PUFAs included 4.98% omega-6 and 3.46% from omega-3. All EMFAs accounted for 78.39%, and the remaining 18.8% was accounted for plasmalogen phospholipids that are comportment of the red blood cell membrane.

In the one-way ANOVA analyses of mean CRP by tertile (T) of EMFAs (Table 4.3), higher mean CRP was associated with tertile 3 (T3) vs. tertile 1 (T1) of palmitic (p= 0.053), palmitoleic acid (p= <0.001), eicosadienoic acid (p= <0.005), dihomo-y-linolenic acid (DGLA) (p= <0.009), and docosapentaenoic acid (DPA-6)

(p= <0.002). Lower mean CRP levels were found with T3 vs. T1 of margaric acid (p= <0.001), arachidic acid (p= 0.001), and linoleic (p=0.05).

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risk for elevated plasma CRP across the EMFA tertiles, are shown in Table 4.4. In a multiple logistic regression analysis that controlled for BMI, smoking, age, education, and gender shown in Table 4.4, the estimated relative risk (adjusted OR (aOR) and 95% confidence intervals (CIs)) for having elevated CRP levels in T3 vs. T1 of total EMFA level was increased for palmitoleic acid (aOR=1.7 [95%CI 1.3-2.2]), nervonic acid (aOR=1.3 [95%CI 1.0-1.6]), DGLA (aOR=1.5 [95%CI 1.2-1.9]), DPA-6 (aOR=0.1.3 [95%CI 1.0- 1.6]), and Docosahexaenoic acid (DHA) (aOR=1.2 [95%CI 1.0- 1.6]). In contrast, the estimated relative risk for having elevated CRP levels was decreased in T3 vs. T1 of margaric acid (aOR=0.67 [95%CI 0.53- 0.89]), stearic acid (aOR=0.78 [95%CI 0.60- 0.99]), and arachidic acid (aOR=0.69 [95%CI 0.53- 0.88]).

When the data were stratified by gender, palmitic acid, palmitoleic acid, and DGLA were more strongly associated with increased risk of elevated CRP risk among women (aOR=1.5 [95%CI 1.1-2.1]), (aOR=1.9 [95%CI 1.3- 2.7]), and (aOR=1.5 [95%CI 1.1-2.2]), respectively, compared to men. Inversely, margaric acid and stearic acid were more strongly associated with reduced risk of elevated CRP in women (aOR=0.57 [95%CI 0.42- 0.80]) and (aOR=0.67 [95%CI 0.48- 0.93]), respectively, than among men. Lastly, arachidic acid was associated with decreased risk of elevation CRP (aOR=0.66 [95%CI 0.44- 0.97]) in both men and (aOR=0.67 [95%CI 0.49- 0.93]) in women.

While the associations between erythrocytes fatty acids and risk of elevated CRP appeared to be stronger in women and not among men, there was not a

significant multiplicative interaction between these erythrocytes fatty acids and CRP elevation ($p > 0.05$).

Discussion

This study provides evidence that erythrocyte membrane fatty acids composition influence the risk of systemic inflammation among participants in the CCMS. Higher levels of palmitoleic acid and nervonic acid both MUFAs, and dihomo-y-linolenic acid, DPA-6, and DHA, all PUFAs, were associated with increased risk of elevation of CRP. Increased levels of margaric acid, stearic acid, and arachidic acid, all saturated FAs, were associated with a lower risk of CRP elevation. None of the other erythrocyte membrane FAs were significantly associated with CRP. These associations were found to be stronger for women vs. men. High level of arachidic acid an SFA was associated with a reduced the risk of elevated CRP among both men and women.

The results of a higher composition of erythrocyte membrane saturated fatty acids and lower CRP risk are consistent with other studies of margaric acid [51-53], but to our knowledge, no other study has examined the association between arachidic acid and inflammatory biomarkers. Until now, the mechanisms of margaric acid as an anti-inflammatory have not been well understood [51], and one observational study reported that the proportion of margaric acid was correlated negatively with inflammatory biomarkers in men and women [52]. Similarly, Wang and Fernandes demonstrated that margaric acid was associated with lower CRP levels among morbid obese patients [51] and adolescents [54].

Findings from studies testing for the association between inflammatory biomarkers and stearic acid have also been inconsistent. In human feeding trials, high levels of stearic acid up-regulates interleukin-6 (IL-6) [55, 56], which is the primary

regulatory agent for CRP [57, 58]. In relevant human tissue culture studies, it was found that high level of stearic acid increased intercellular adhesion molecule (ICAM-1) expression, which activates inflammation pathways [59]. Similarly, thioglycollate-elicited mouse peritoneal macrophages (MPMs) were collected from knockout mice and showed that a high level of stearic acid up regulates pro-inflammatory signals causing ER stress–mediated apoptosis [60]. With this in mind, many potentially therapeutic and anti-inflammatory effects have also been proposed for stearic acid. Stearic acid attenuated cholestasis-induced liver injury in rats and had an anti-inflammatory effect by reducing Alpha-smooth muscle actin (alpha-SMA); alpha-SMA is the actin isoform that predominates in vascular smooth-muscle cells and plays an important role in fibrogenesis [61],which produces fibrogenic cytokine leading to a transforming of growth factor beta-1 (TGF-β1) production [62]. Moreover, a copolymer of fatty acids, composed of oleic acid, palmitic acid and stearic acid, called Ara 3000 beta reduced osteoarthritis symptoms due to the FAs anti-inflammatory effects in human [63] and dogs [64].

Findings from studies associating palmitoleic acid and inflammation have also been inconsistent. Previously, a serum FA pattern with high palmitoleic acid was linked to elevated CRP among Swedish elderly [65]. Two clinical trials reported that palmitoleic acid composition elevated inflammatory biomarkers [66] leading to an increase in the risk of metabolic syndrome [66]. The same result was found when diet and a low-density lipoprotein (LDL) receptor genotype were examined on macrophage foam cell formation within the peritoneal cavities of mice [67]. In a human adipocyte cell culture, palmitoleic acid induced pro-inflammatory effect by activating a Toll-like receptor-4/nuclear factor-kB (TLR-4/NF-kB) pathway [68]. In contrast, a prospective cohort study of 86 ambulatory patients and 45 healthy subjects

reported that palmitoleic acid was not associated with inflammation [69]. Until now, no study to our knowledge has investigated the effect of monounsaturated nervonic acid on plasma CRP level or any other inflammatory biomarkers.

Our results are not consistent with the reported anti-inflammatory effect of DGLA which is an omega-6 FA [39, 40, 70]. Metabolic studies reported that gamma-linolenic acid (GLA) fatty acids convert to dihomo-γ-linolenic acid (DGLA) by competing with arachidonic acid (AA) to express an anti-inflammatory effect in cells by inhibiting enzymes that come from the breakdown of AA accumulation in cells [71, 72]. This inhibition reduces prostaglandin cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and leukotrienes [73] causing a reduction of inflammatory molecules [74, 75] in lung function, autoimmune conditions, cardiovascular disease, and diabetes [71, 72].

Our results confirmed the limited evidence that investigated Docosapentaenoic acid n6 (DPA-6) fatty acids [76, 77]. In rats, a high administration of DHA lowered the conversion of DPA-6 to arachidonic acid (AA) [77].

There is literature on using plasma and erythrocyte levels to reflect the measured dietary intake of fatty acids [43, 78, 79]. Due to the different structure and function properties of plasma and erythrocyte membrane, it is not surprising that level and the relevant composition of the FA is different between these two compartments of the blood [80]. Plasma measurement is considered the most immediate biomarker for each individual fatty acid [81, 82] because it reflects the dietary intake of the previous hours (triglyceride) or the past few days (cholesterol ester and phospholipid fatty acids). Erythrocyte measures of fatty acids are of interest for fatty acid analysis [82]. The half-life of erythrocytes has been estimated to be 120 days, which is much longer than that of plasma lipoproteins. Thus, erythrocytes reflect fat intake over

longer term [83, 84]. Sun et al. reported moderate-to-strong correlations between the dietary intake of n-3 fatty acids from marine origin and trans fatty acids and their levels in erythrocytes and plasma and the correlations with dietary intakes were stronger for erythrocytes than for plasma [85]. Because of these differences in long term stability FA analysis of erythrocytes is more suitable to test the association between long term FAs intake and inflammatory biomarkers [27, 86].

Regarding fatty acid composition in human subjects, Petersson et al. [65] reviewed compilation of a studies on total plasma fatty acid composition in the elderly, and among the fatty acids analyzed, linoleic acid, oleic acid, and palmitic acid had the highest proportions, respectively. In the present study, palmitic acid and stearic acid had the highest proportions, respectively. Other studies with elderly showed a similar pattern compared to the results found in the current work, with high amounts of SFA and low amount of PUFA [87, 88] in the erythrocyte membrane.

The association between plasma CRP levels and DHA composition is unusual and requires further investigation. The literature on the association between DHA and high risk of CRP bring mixed results. Over the last decade, many biochemical and observational studies have suggested that DHA works as anti-inflammatory, which is not in line with our results [89-92]. Many observational studies reported that high consumption of omega-3 including DHA did not affect CRP levels among type 2 diabetics, healthy individuals, and elderly [93-97]. Recently, a study of double blinded randomized trial of 2425 patients found that there was no effect of high consumption of EPA-DHA on CRP levels [98]. Ours is the first study to our knowledge that showed evidence of increased CRP risk among elderly participants who have higher levels of erythrocyte DHA. Biochemical studies have suggested that FAs compete for the same set of enzymes to form a long chain of PUFA derivatives

[13, 18, 99, 100]. Despite this finding, more studies are needed to confirm and explain the association between total DHA fatty acid composition and CRP levels, particularly in the elderly.

In our analysis, we observed CRP levels were higher in women compared with men. Piéroni et al. reported that CRP values were higher among women than men when they measured CRP levels in healthy adults in Paris [101] and Rifai and Ridker reported the same results when they measured CRP levels in healthy men and women in the United States [102]. The relationship between gender and erythrocyte membrane fatty acids needs further work, but it appears that erythrocyte membrane fatty acids have a greater effect on CRP levels in women compared to men.

To our knowledge, this is the first study that examines the multiplicative interaction between erythrocyte fatty acids and risk of elevated CRP. Thus, further studies are needed to confirm our results.

Our study has several key strengths: the study is population-based of the elderly and relatively robust against selection bias because of higher participation rates. EMFA assays also reflect the combination of dietary factors, metabolic and genetic effects. CRP was used to assess low grade systemic inflammation because a large amount of work using CRP has been done over the last two decades to assess inflammation levels in humans. Thus, our results are more valuable and reliable thru the use of CRP levels and a large number of study participants. The results of our analysis must be considered in light of its limitations chiefly that the analysis was cross-sectional as the Cache County Memory Study did not have a collection of blood for CRP at the Wave 1 baseline examination that would allow for a prospective study of CRP levels and subsequent outcomes.

In this Cache County cohort of elderly participants, increasing levels of palmitoleic acid and nervonic acid, both MUFAs, and dihomo-y-linolenic acid, docosapentaenoic acid n6, docosahexaenoic acid, all PUFAs, were associated with elevates CRP. Conversely, increasing levels of margaric acid, stearic acid, and arachidic acid, all SFAs, were related to decreased CRP. The relationship between CRP and another FA was not significant even after controlling the covariates.

In summary, our results suggest that the higher SFA composition of EMFAs including margaric, stearic, and arachidic fatty acids are anti-inflammatory. Concomitantly, our finding suggests that higher levels of the MUFAs palmitoleic and nervonic and the PUFAs DGLA, DPA-6 and DHA are pro-inflammatory. Further prospective and experimental studies should be conducted to gain a better understanding of the controversies regarding dietary intake of FAs, cell membrane FA composition and systemic inflammation.

Table 4.1: Demographic characteristics by level of C- reactive protein (CRP) in the

Cache County Study on Memory, Health and Aging in Wave 3 (N= 2031).

Characteristic	Plasma CRP composition (mg/L)		p-value[1]
	<3.0 (mg/L)	>3.0 (mg/L)	
Gender			
- Male (%)	63.5	36.5	<0.001
- Female (%)	54.9	45.1	
Less than high school education (%)	54.9	61.8	0.001
More than high school education (%)	45.1	38.2	
Age in years (SD)[2]	73.0± 5.4	73.1± 5.5	0.480
Body mass index (kg/m^2) (SD) [2]	25.9± 4.0	27.2± 4.4	<0.001
Current smoke (%)[3]	1.4	2.9	0.042
Current alcohol (%)[3]	4.4	3.7	0.442
At least one APOE e4 allele (%)	35.8	26.2	<0.001
Diagnosed with diabetes (%)	17.4	20.0	0.078
Diagnosed with stroke (%)	7.3	10.1	0.018
Diagnosed with heart attack (%)	14.4	16.0	0.178

[1] p-values were obtained by using the Chi-square test for CRP (low vs. high) for categorical variables and One-way analysis of variance (ANOVA) for continuous variables.

[2] Means ± standard deviation (SD).

[3] A current smoker was defined as a subject who reported currently smoking; a current drinker was defined as a subject who reported currently drinking alcohol.

Table 4.2: Median erythrocyte membrane fatty acid (FA) (range) percent composition in serum in the Cache County Memory Study (n= 1835).

RBC FAs[1]	Type[2]	Molecular Formula	C:D[3]	Percent concentration	Food Sources	References
Pentadecanoic acid	SFA	$C_{15}H_{30}O_2$	15:0	0.14 (0.04- 0.59)	Cow milk	[103]
Palmitic acid	SFA	$C_{16}H_{32}O_2$	16:0	23.3 (7.75- 36.21)	Meat, including poultry, beef and game meats	[104]
Margaric acid	SFA	$C_{17}H_{34}O_2$	17:0	0.40 (0.12- 1.9)	Cow milk	[105]
Stearic acid	SFA	$C_{18}H_{36}O_2$	18:0	19.6 (6.3- 33.3)	Meat, poultry, fish, grain products, and milk/ milk products, cocoa butter, lard, and butter	[56]
Arachidic acid	SFA	$C_{20}H_{40}O_2$	20:0	0.31 (0.08- 1.32)	Peanut oil (1.1%−1.7%) and corn oil	[106]
Behenic acid	SFA	$C_{22}H_{44}O_2$	22:0	1.1 (0.06- 3.9)	Peanut oil and peanut butter	[107]
Lignoceric acid	SFA	$C_{24}H_{48}O_2$	24:0	2.6 (0.11- 6.8)	Peanut oil	[106]
Palmitoleic acid (Omega 7)	MUFA	$C_{16}H_{30}O_2$	16:1	0.11 (0.01- 0.59)	Animal oils, vegetable oils, marine oils, macadamia oil, and sea buckthorn oil	[108]
Oleic acid (%)	MUFA	$C_{18}H_{34}O_2$	18:1	0.42 (0.07- 1.72)	Vegetable oils such as olive, canola and sunflower, nut oils, meat, poultry, and cheese	[109]
Gondoic acid (Omega 9)	MUFA	$C_{20}H_{38}O_2$	20:1	3.4 (0.09- 6.7)	Plant oils and nuts	[110]
Erucic acid (Omega 9)	MUFA	$C_{22}H_{42}O_2$	22:1	2.8 (0.23- 4.2)	Wallflower seed and mustered oil	[111]
Nervonic acid	MUFA	$C_{24}H_{46}O_2$	24:1	1.3 (0.28- 3.9)	Salmon, yellow mustard seed, and flaxseed	[112]

Vaccenic acid	TFA	$C_{18}H_{34}O_2$	18:1	0.43 (0.07- 0.89)	Meat and dairy fat such as milk, and buttr	[113]
1104Linoleic acid	PUFA	$C_{18}H_{32}O_2$	18:2	4.7 (1.17- 8.0)	Vegetable oils such as flaxseed (linseed) oil, canola (rapeseed) oil, and soybean oil.	[114]
a-Linolenic acid (ALA)	PUFA	$C_{18}H_{30}O_2$	18:3	0.06 (0.01- 0.37)	Fish oils, flaxseed oil, and in canola, soy, perilla, and walnut oils	[21]
Eicosadienoic acid (Omega 6)	PUFA	$C_{20}H_{36}O_2$	20:2	0.11 (0.02- 0.63)	Poultry, nuts, and cereals	[115]
Dihomo-y-linolenic acid (DGLA) (Omega 6)	PUFA	$C_{18}H_{30}O_2$	20:3	0.62 (0.14- 1.41)	Animal-source foods, such as meat, egg, fish.	[116]
Arachidonic acid	PUFA	$C_{20}H_{32}O_2$	20:4	6.6 (1.57- 10.17)	Chicken, eggs, and beef	[117]
Eicosapentaenoic acid (EPA) (Omega 3)	PUFA	$C_{20}H_{30}O_2$	20:5	0.18 (0.03- 1.2)	Fish oil, cod liver, herring, mackerel, and sardine	[118]
Adrenic acid (Omega 6)	PUFA	$C_{22}H_{36}O_2$	22:4	1.4 (0.43- 2.3)	Poultry, nuts, cereals, and whole grain breads	[115]
Docosapentaenoic acid n3 (DPA-3) (Omega 3)	PUFA	$C_{22}H_{34}O_2$	22:5	1.0 (0.17- 2.0)	Bearded seal (Alaska Native), fish oil, menhaden, salmon, and sardine	[119]
Docosapentaenoic acid n6 (DPA-6) (Omega 6)	PUFA	$C_{22}H_{34}O_2$	22:5	0.28 (0.05- 0.76)	Fish and fish oils	[119]
Docosahexaenoic acid (DHA) (Omega 3)	PUFA	$C_{22}H_{32}O_2$	22:6	1.6 (0.22- 5.3)	Fish oils, eggs and meats	[118]

[1] FA are presented as percentage of FA analyzed.

[2] SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; TFA, trans fatty acids; PUFA, polyunsaturated fatty acids.

[3] Number of carbon atoms: number of double bonds.

Table 4.3: Mean of plasma biomarker concentration of C-reactive protein (CRP) across tertiles of erythrocyte membrane fatty acid in the Cache County Memory Study.

RBC Fatty acids	Type[1]	Mean plasma CRP concentration (mg/L)[2] by tertiles (T1-T3) of erythrocyte membrane fatty acid			p-value[3]
		T1	T2	T3	
Pentadecanoic acid	SFA	4.8± 7.2	4.8± 7.2	4.2± 7.6	0.125
Palmitic acid	SFA	4.6± 7.3	4.2± 6.9	5.1± 8.2	0.053
Margaric acid	SFA	5.2± 7.6	4.5± 6.9	4.1± 7.9	<0.001
Stearic acid	SFA	4.8± 7.4	4.7± 7.3	4.2± 7.7	0.105
Arachidic acid	SFA	4.8± 7.0	5.0± 8.4	4.0± 6.9	0.001
Behenic acid	SFA	4.6± 7.0	4.9± 8.4	4.2± 6.9	0.244
Lignoceric acid	SFA	4.6± 8.0	4.9± 7.2	4.3± 7.3	0.103
Palmitoleic acid	MUFA	4.2± 8.2	4.4± 6.5	5.1± 7.7	<0.001
Oleic acid	MUFA	4.7± 7.1	4.5± 7.3	4.5± 8.1	0.184
Gondoic acid	MUFA	4.4± 6.5	4.8± 8.2	4.6± 7.7	0.266
Erucic acid	MUFA	4.1± 6.3	4.8± 8.3	4.9± 7.7	0.052
Nervonic acid	MUFA	4.4± 8.0	4.2± 5.6	5.1± 8.5	0.149
Vaccenic acid	TFA	4.5± 7.3	4.7± 7.6	4.6± 7.6	0.426
Linoleic acid	PUFA	5.1± 8.3	4.4± 8.1	4.2± 5.7	0.050
a-Linolenic acid (ALA)	PUFA	4.7± 8.0	4.8± 8.2	4.2± 6.1	0.791
Eicosadienoic acid	PUFA	4.9± 8.1	3.8± 6.0	5.1± 8.2	0.005
Dihomo-y-linolenic acid (DGLA)	PUFA	4.6± 8.2	4.5± 7.2	4.7± 6.9	0.009
Arachidonic acid	PUFA	3.9± 5.3	4.9± 9.0	4.9± 7.6	0.127
Eicosapentaenoic acid (EPA)	PUFA	5.3± 9.3	4.4± 6.5	4.1± 6.2	0.900
Adrenic acid	PUFA	4.1± 6.3	4.8± 7.6	4.9± 8.3	0.357
Docosapentaenoic acid (DPA-3)	PUFA	5.0± 8.0	4.4± 6.8	4.3± 7.6	0.090
Docosapentaenoic acid (DPA-6)	PUFA	4.3± 7.3	4.2± 6.7	5.3± 8.0	0.002
Docosahexaenoic acid (DHA)	PUFA	4.7± 8.6	4.7± 7.6	4.3± 6.0	0.386

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; TFA, trans fatty acids; PUFA, polyunsaturated fatty acids.
[2] Means± standard deviation (SD)
[3] p-values were obtained by using Analysis of Variance (ANOVA)

Table 4.4: Odds ratio of clinically relevant elevation of CRP (> 3.00 mg/L) by tertiles of erythrocyte membrane fatty acid in the Cache County Memory (n= 1844).

RBC Fatty acids	Type[1]	T1	T2	T3	P-linear trend[2]
Pentadecanoic acid	SFA	1.00 [reference]	1.2 (0.97- 1.5)	1.0 (0.85- 1.4)	0.497
Palmitic acid	SFA	1.00 [reference]	0.90 (0.70- 1.1)	1.2 (0.95- 1.6)	0.121
Margaric acid	SFA	1.00 [reference]	0.92 (0.73- 1.2)	0.68 (0.53- 0.89)	0.004
Stearic acid	SFA	1.00 [reference]	0.90 (0.72- 1.1)	0.78 (0.60- 0.99)	0.040
Arachidic acid	SFA	1.00 [reference]	0.89 (0.70- 1.1)	0.69 (0.53- 0.88)	0.002
Behenic acid	SFA	1.00 [reference]	1.0 (0.81- 1.3)	0.89 (0.70- 1.1)	0.294
Lignoceric acid	SFA	1.00 [reference]	1.2 (0.98- 1.6)	1.0 (0.81- 1.3)	0.840
Palmitoleic acid	MUFA	1.00 [reference]	1.3 (0.98- 1.6)	1.7 (1.3- 2.2)	<0.001
Oleic acid	MUFA	1.00 [reference]	0.98 (0.77- 1.2)	0.80 (0.63- 1.0)	0.089
Gondoic acid	MUFA	1.00 [reference]	1.0 (0.79- 1.2)	0.90 (0.70- 1.1)	0.414
Erucic acid	MUFA	1.00 [reference]	1.1 (0.85- 1.3)	1.0 (0.82- 1.3)	0.748
Nervonic acid	MUFA	1.00 [reference]	1.1 (0.86- 1.4)	1.3 (1.0- 1.6)	0.038
Vaccenic acid	TFA	1.00 [reference]	1.1 (0.89- 1.4)	1.1 (0.83- 1.3)	0.606
Linoleic acid	PUFA	1.00 [reference]	0.80 (0.63- 1.0)	1.0 (0.81- 1.3)	0.695
a-Linolenic acid (ALA)	PUFA	1.00 [reference]	1.1 (0.90- 1.5)	1.1 (0.87- 1.4)	0.415
Eicosadienoic acid	PUFA	1.00 [reference]	0.83 (0.65- 1.0)	1.1 (0.86- 1.3)	0.435
Dihomo-y-linolenic acid (DGLA)	PUFA	1.00 [reference]	1.3 (0.99- 1.6)	1.5 (1.2- 1.9)	0.001
Arachidonic acid	PUFA	1.00 [reference]	1.1 (0.84- 1.3)	1.0 (0.79- 1.2)	0.984
Eicosapentaenoic acid (EPA)	PUFA	1.00 [reference]	1.2 (0.96- 1.5)	1.1 (0.85- 1.4)	0.510
Adrenic acid	PUFA	1.00 [reference]	1.1 (0.89- 1.4)	0.98 (0.76- 1.2)	0.818
Docosapentaenoic acid n3 (DPA-3)	PUFA	1.00 [reference]	0.90 (0.70- 1.1)	0.95 (0.75- 1.2)	0.681
Docosapentaenoic acid n6 (DPA-6)	PUFA	1.00 [reference]	0.99 (0.77- 1.2)	1.3 (1.0- 1.6)	0.026
Docosahexaenoic acid (DHA)	PUFA	1.00 [reference]	1.4 (1.1- 1.8)	1.2 (1.0- 1.6)	0.039

Total n-3 fatty acids[3]	PUFA	1.00 [reference]	1.16 (0.91- 1.5)	1.06 (0.84- 1.4)	0.605
Total n-6 fatty acids[3]	PUFA	1.00 [reference]	0.90 (0.70- 1.1)	1.02 (0.80- 1.30)	0.810
Total n-6/ n-3 fatty acids	PUFA	1.00 [reference]	0.95 (0.74- 1.2)	1.06 (0.82- 1.4)	0.640

[1] SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; TFA, trans fatty acids; PUFA, polyunsaturated fatty acids.

[2] Values are 95% Confidence Interval in parentheses (all such values). Adjusted variables in multivariate models included body mass index (kg/m2, continuous), smoking (never, former, current), age, in years (65-74, 75-84, 85+), education levels (less than high school, high school, more than high school), and gender (male, female).

[3] Total n-3 fatty acids included ALA, EPA, DPA-3, and DHA; Total n-6 fatty acids included linoleic acid, eicosadienoic acid, DGLA, adrenic, and DPA-6.

Table 4.5: Odds ratio of clinically relevant elevation of CRP (> 3.00 mg/L) by tertiles of erythrocyte membrane fatty acid in the Cache County Memory stratified by gender.

RBC Fatty acids	Type[1]	Male				Female			
		T1	T2	T3	P-linear trend[2]	T1	T2	T3	P-linear trend[2]
Pentadecanoic acid	SFA	1.00 [reference]	0.93 (0.63- 1.3)	1.00 (0.70- 1.4)	0.209	1.00 [reference]	1.40 (1.0- 2.0)	1.10 (0.79- 1.5)	0.520
Palmitic acid	SFA	1.00 [reference]	0.66 (0.45- 0.95)	0.88 (0.61- 1.2)	0.459	1.00 [reference]	1.10 (0.81- 1.5)	1.50 (1.1- 2.1)	0.015
Margaric acid	SFA	1.00 [reference]	1.30 (0.85- 1.8)	0.91 (0.61- 1.3)	0.557	1.00 [reference]	0.78 (0.57- 1.0)	0.57 (0.42- 0.80)	0.001
Stearic acid	SFA	1.00 [reference]	1.10 (0.72- 1.5)	0.92 (0.62- 1.3)	0.631	1.00 [reference]	0.82 (0.60- 1.1)	0.67 (0.48- 0.93)	0.019
Arachidic acid	SFA	1.00 [reference]	0.76 (0.52- 1.1)	0.66 (0.44- 0.97)	0.035	1.00 [reference]	0.98 (0.71- 1.3)	0.67 (0.49- 0.93)	0.021
Behenic acid	SFA	1.00 [reference]	0.90 (0.62- 1.3)	0.89 (0.62- 1.3)	0.571	1.00 [reference]	1.10 (0.80- 1.5)	0.85 (0.61- 1.2)	0.375
Lignoceric acid	SFA	1.00 [reference]	1.00 (0.69- 1.5)	0.97 (0.67- 1.4)	0.883	1.00 [reference]	1.40 (1.0- 1.9)	1.00 (0.76- 1.4)	0.717
Palmitoleic acid	MUFA	1.00 [reference]	1.20 (0.83- 1.7)	1.30 (0.92- 2.0)	0.101	1.00 [reference]	1.30 (0.96- 1.9)	1.90 (1.3- 2.7)	<0.001
Oleic acid	MUFA	1.00 [reference]	0.95 (0.65- 1.3)	0.78 (0.53- 1.1)	0.222	1.00 [reference]	0.98 (0.71- 1.3)	0.83 (0.60- 1.1)	0.270
Gondoic acid	MUFA	1.00 [reference]	0.93 (0.64- 1.3)	0.99 (0.68- 1.4)	0.980	1.00 [reference]	1.10 (0.79- 1.5)	0.84 (0.61- 1.1)	0.300
Erucic acid	MUFA	1.00 [reference]	1.10 (0.72- 1.5)	1.30 (0.90- 1.9)	0.140	1.00 [reference]	1.10 (0.79- 1.5)	0.89 (0.64- 1.2)	0.461
Nervonic acid	MUFA	1.00 [reference]	0.79 (0.54- 1.2)	1.10 (0.79- 1.6)	0.480	1.00 [reference]	1.30 (0.98- 1.8)	1.40 (1.0- 1.9)	0.042
Vaccenic acid	TFA	1.00 [reference]	1.10 (0.76- 1.6)	1.00 (0.70- 1.4)	0.893	1.00 [reference]	1.10 (0.81- 1.5)	1.00 (0.77- 1.4)	0.672
Linoleic acid	PUFA	1.00 [reference]	0.78 (0.52- 1.1)	1.10 (0.71- 1.5)	0.701	1.00 [reference]	0.82 (0.60- 1.1)	1.10 (0.76- 1.4)	0.774
a-Linolenic acid (ALA)	PUFA	1.00 [reference]	1.30 (0.95- 1.9)	1.10 (0.76- 1.6)	0.488	1.00 [reference]	1.00 (0.71- 1.3)	1.10 (0.79- 1.5)	0.554
Eicosadienoic acid	PUFA	1.00 [reference]	0.57 (0.38- 0.84)	0.95 (0.65- 1.3)	0.791	1.00 [reference]	1.10 (0.79- 1.5)	1.30 (0.90- 1.7)	0.169
Dihomo-y-linolenic acid (DGLA)	PUFA	1.00 [reference]	1.20 (0.83- 1.7)	1.30 (0.91- 1.9)	0.128	1.00 [reference]	1.20 (0.92- 1.7)	1.50 (1.1- 2.2)	0.005
Arachidonic acid	PUFA	1.00 [reference]	1.10 (0.73- 1.5)	1.20 (0.83- 1.7)	0.307	1.00 [reference]	1.10 (0.77- 1.4)	0.90 (0.64- 1.2)	0.453
Eicosapentaenoic acid (EPA)	PUFA	1.00 [reference]	1. 20 (0.96- 1.5)	1.10 (0.85- 1.4)	0.510	1.00 [reference]	1.00 (0.71- 1.3)	1.10 (0.79- 1.5)	0.554
Adrenic acid	PUFA	1.00 [reference]	1.10 (0.75- 1.6)	1.10 (0.76- 1.6)	0.566	1.00 [reference]	1.10 (0.82- 1.5)	0.88 (0.63- 1.2)	0.471

Docosapentaenoic acid n3 (DPA-3)	PUFA	1.00 [reference]	0.79 (0.52- 1.1)	1.10 (0.77- 1.6)	0.422	1.00 [reference]	0.95 (0.69- 1.2)	0.79 (0.57- 1.1)	0.169
Docosapentaenoic acid n6 (DPA-6)	PUFA	1.00 [reference]	0.93 (0.63- 1.3)	1.40 (0.97- 2.1)	0.077	1.00 [reference]	1.10 (0.76- 1.4)	1.20 (0.91- 1.7)	0.156
Docosahexaenoic acid (DHA)	PUFA	1.00 [reference]	1.30 (0.95- 2.0)	1.20 (0.85- 1.8)	0.235	1.00 [reference]	1.40 (1.0- 2.1)	1.30 (0.95- 1.8)	0.118
Total n-3 fatty acids[3]	PUFA	1.00 [reference]	1.2 (0.78- 1.7)	1.2 (0.81- 1.7)	0.391	1.00 [reference]	1.14 (0.83- 1.6)	0.98 (0.71- 1.4)	0.938
Total n-6 fatty acids[3]	PUFA	1.00 [reference]	1.1 (0.75- 1.6)	1.06 (0.72- 1.5)	0.760	1.00 [reference]	0.78 (0.56- 1.1)	1.02 (0.74- 1.4)	0.867
Total n-6/ n-3 fatty acids	PUFA	1.00 [reference]	0.93 (0.62- 1.4)	1.1 (0.72- 1.5)	0.757	1.00 [reference]	0.98 (0.70- 1.4)	1.1 (0.77- 1.5)	0.661

[1] SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; TFA, trans fatty acids; PUFA, polyunsaturated fatty acids.

[2] Values are 95% Confidence Interval in parentheses (all such values). Adjusted variables in multivariate models included body mass index (kg/m2, continuous), smoking (never, former, current), age, in years (65-74, 75-84, 85+), education levels (less than high school, high school, more than high school), and gender (male, female).

[3] Total n-3 fatty acids included ALA, EPA, DPA-3, and DHA; Total n-6 fatty acids included linoleic acid, eicosadienoic acid, DGLA, adrenic, and DPA-6.

Table 4.6: Spearman rank order correlation coefficients of the dietary intake of total fats, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, omega6:omega3 ratio, CRP and with erythrocyte membrane fatty acid in the Cache County Memory Study.

Erythrocyte membrane fatty acid	Correlation with total fats (p-values)	Correlation with SFA (p-values)	Correlation with MUFA (p-values)	Correlation with PUFA (p-values)	Correlation with Omega 3 (p-values)	Correlation with Omega 6 (p-values)	Correlation with Omega6:omega3 (p-values)	Correlation with CRP (p-values)
Saturated fatty acids								
Pentadecanoic acid	0.029 (0.267)	0.176[**] (<0.001)	0.023 (0.362)	-0.192[**] (<0.001)	-0.049 (0.057)	-0.206[**] (<0.001)	-0.123[**] (<0.001)	-0.031 (0.190)
Palmitic acid	-0.071[**] (0.006)	-0.025 (0.339)	-0.069[**] (0.007)	-0.069[**] (0.008)	-0.020 (0.427)	-0.068 (0.008)	-0.069[**] (0.008)	0.053[*] (0.023)
Margaric acid	0.000 (0.985)	0.016 (0.525)	-0.020 (0.449)	-0.070[**] (0.007)	-0.033 (0.197)	0.087[**] (0.001)	-0.059[*] (0.024)	0.118[**] (<0.001)
Stearic acid	-0.056[*] (0.029)	0.035 (0.170)	0.042 (0.101)	0.025 (0.331)	0.016 (0.537)	0.014 (0.595)	0.024 (0.367)	-0.041 (0.080)
Arachidic acid	0.022 (0.398)	0.011 (0.669)	0.011 (0.667)	0.006 (0.821)	0.029 (0.254)	-0.001 (0.969)	-0.017 (503)	-0.080[**] (0.001)
Behenic acid	0.050 (0.054)	0.046 (0.074)	0.032 (0.218)	0.006 (0.811)	0.011 (0.673)	0.004 (0.865)	-0.007 (0.786)	-0.043 (0.063)
Lignoceric acid	0.036[**] (0.157)	0.017 (0.501)	0.036 (0.157)	0.020 (0.439)	0.014 (0.597)	0.017 (0.517)	-0.009 (0.742)	-0.013 (0.567)
Monounsaturated fatty acids								
Palmitoleic acid	-0.175[**] (<0.001)	-0.067[**] (0.009)	-0.159 (<0.001)	-0.208[**] (<0.001)	-0.059[**] (0.023)	-0.198 (<0.001)	-0.088[**] (0.001)	0.146[**] (<0.001)
Oleic acid	0.044 (0.085)	0.016 (0.539)	0.005 (0.839)	0.070[**] (0.006)	0.018 (0.484)	0.066[*] (0.010)	0.039 (0.133)	-0.059[*] (0.012)
Gondoic acid	-0.061[*] (0.017)	-0.042 (0.107)	0.078[**] (0.002)	-0.077[**] (0.003)	-0.027 (0.293)	-0.072[**] (0.005)	-0.021 (0.424)	-0.025 (0.282)
Erucic acid	0.032 (0.215)	0.014 (0.583)	0.039 (0.134)	0.039 (0.132)	-0.018 (0.486)	0.045 (0.080)	0.041 (0.112)	0.049[*] (0.035)
Nervonic acid	-0.026 (0.320)	-0.070[**] (0.007)	-0.015 (0.558)	0.022 (0.385)	0.025 (0.332)	0.023 (0.377)	-0.020 (0.454)	0.035 (0.135)
Monounsaturated fatty acids trans								
Vaccenic acid	-0.063[*] (0.015)	-0.081[**] (0.002)	-0.059[*] (0.022)	0.025 (0.341)	0.021 (0.416)	0.016 (0.531)	-0.023 (0.368)	0.013 (0.572)

Polyunsaturated fatty acids							
Linoleic acid	0.120** (<0.001)	0.024 (0.349)	0.099** (<0.001)	0.150** (<0.001)	0.036 (0.163)	0.152** (<0.001)	0.086** (0.001)	-0.033** (0.157)
a-Linolenic acid (ALA)	-0.062* (0.017)	-0.114** (<0.001)	-0.082 (0.001)	0.035 (0.177)	0.072** (0.005)	0.046 (0.075)	-0.019 (0.456)	-0.004 (0.867)
Eicosadienoic acid	-0.025 (0.338)	-0.169** (<0.001)	-0.042 (0.102)	0.179** (<0.001)	0.179** (<0.001)	0.071** (0.006)	0.183** (<0.001)	0.002 (0.993)
Dihomo-y-linolenic acid (DGLA)	-0.055* (0.032)	-0.026 (0.311)	-0.031 (0.232)	-0.055* (0.033)	-0.047 (0.068)	-0.052* (0.044)	0.078** (0.003)	0.093** (<0.001)
Arachidonic acid	0.027 (0.294)	0.006 (0.810)	0.031 (0.226)	0.043 (0.094)	-0.023 (0.381)	0.047 (0.067)	0.050 (0.053)	0.044 (0.061)
Eicosapentaenoic acid (EPA)	-0.123** (<0.001)	-0.099** (<0.001)	-0.090** (<0.001)	-0.075** (0.004)	0.116** (<0.001)	-0.097 (<0.001)	-0.183** (<0.001)	0.018 (0.434)
Adrenic acid	0.108** (<0.001)	0.080** (0.002)	0.091 (<0.001)	0.072** (0.005)	-0.065** (0.011)	-0.069 (0.011)	0.069** (0.007)	0.023 (0.318)
Docosapentaenoic acid (DPA-3)	-0.038 (0.141)	-0.029 (0.262)	-0.024 (0.347)	-0.011 (0.660)	0.063* (0.014)	-0.026 (0.322)	-0.067* (0.010)	-0.060* (0.010)
Docosapentaenoic acid (DPA-6)	0.084** (0.001)	0.128** (<0.001)	0.081 (0.002)	-0.028 (0.282)	0.122** (<0.001)	-0.017 (0.514)	-0.085** (0.001)	0.079* (0.001)
Docosahexaenoic acid (DHA)	-0.146** (<0.001)	-0.193** (<0.001)	-0.108** (<0.001)	0.023 (0.377)	0.142** (<0.001)	0.007 (0.780)	-0.150** (<0.001)	0.022 (0.348)

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
Note: Nutrients in which correlations are different between Saturated fats (SFA), Monounsaturated (MUFA), Polyunsaturated (PUFA), and C-reactive protein (CRP).

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CHAPTER 5

THE ROLE OF ALZHEIMER'S- RELATED GENES IN SYSTEMIC

INFLAMMATION IN THE CACHE COUNTY MEMORY STUDY

Abstract

Objective: To evaluate whether Alzheimer's Disease (AD)-related genes, identified in previous genome-wide association studies, are associated with elevated levels of inflammatory C-reactive protein (CRP) in a prospective, population-based study.

Design: We analyzed data from dementia-free participants in the Cache County Memory Study (CCMS). In a total of 2031 men and women $\geq$ 65 years of age at the baseline, we examined the association between polymorphisms of 20 AD-related genes and biomarker of systemic inflammation.

Results: After controlling multiple covariates, risk of elevated CRP was increased in minor allele homozygotes vs. major allele homozygotes for APOE rs439401 (aOR= 1.4 [95%CI 1.4- 1.7]) and TOMM40 rs157580 (aOR= 1.2 [95%CI 0.96- 1.46]). In contrast, risk of CRP elevation was reduced in minor allele homozygotes for MMP8 rs1892886 (aOR = 0.78 [95%CI 0.64- 0.90]). These and other associations appeared stronger among male than women; risk of elevated CRP in males was increased in minor allele homozygotes for APOE rs439401 (aOR= 1.6 [95%CI 1.1- 2.1]) and TOMM40 rs157580 (aOR= 1.5 [95%CI 1.1- 2.1]) and reduced for MMP8 rs1892886 (aOR = 0.64 [95%CI 0.46- 0.89]), CR1 rs665401 (aOR = 0.60 [95%CI 0.42- 0.84]), CR1 rs3818361 (aOR= 0.43 [95%CI 0.28- 0.66]), and CR1 rs4844609 (aOR = 0.38 [95%CI 0.19- 0.80]).

Conclusions: The AD associated genes APOE, TOMM40, CR1, and MMP8 are associated with altered CRP levels, a marker of systemic inflammation and these associations appear stronger for men compared to women.

Introduction

Alzheimer's disease (AD) is the sixth leading cause of death in the United States [1]. It is the most common form of dementia. In 2015, Alzheimer's disease affected 5.3 million Americans, and it affects 44 million worldwide. Alzheimer's prevalence is 1 in 9 older Americans [1]. Inflammation plays a key role in the pathogenesis of AD [2]. Scientific knowledge is far from complete regarding the relationship between inflammatory biomarkers and AD. However, scientific advances recently have been noticeably changing the understanding of the role of high levels of inflammatory biomarker C-reactive protein (CRP) in AD patients and other chronic diseases [3, 4]. CRP is a plasma protein synthesized by the liver in response to cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α)[5]. A growing number of cross-sectional studies reported that high level of CRP was found in AD patients when they were compared to controls [6-8]. Concomitantly, several observational studies have provided convincing evidence that the low-grade inflammatory process that is indicated by high levels of CRP in older adults correlates with AD risk [9, 10].

Recent large genome-wide association studies (GWAS) have identified many genes/loci that are associated with late-onset Alzheimer's disease (LOAD) including BIN1, CLU, PICALM, MS4A6A, CD33, MS4A4E, CD2AP, CR1, ABCA7, AGTR1, APOE, TOMM40, DTNA, HTR2C, EPHA1, MMP8, MPP7, SORCS1, PPP3R1, and

MAPT/STH [11]. Genetic data reveal that some risks of disease initiation, progression, and severity are linked to different alleles of genes by affecting inflammation pathways. Genetic diversity plays an important role in immunity, inflammation, and inflammatory disease [12].

Genes affecting the risk of systemic inflammation have gathered increasing attention from geneticists and epidemiologists interested in related inflammatory diseases including Alzheimer's disease [13]. APOE (chromosome 19q12-13.2) is known to have a key role in determining the risk of AD. APOE has many polymorphisms including epsilon (ε2, ε3, and ε4), rs439401, and rs4420638 [14]. Functionally, APOE polymorphisms contribute to neuronal development, regeneration, and repair in the central nervous system (CNS) [13, 15]. APOE also plays a major role in the cholesterol and triglyceride metabolism [16-18]. Most studies have reported that ε2 and ε4 have an opposing biological effect on lipid metabolism [19-21].

In regards of inflammation, APOE ε4 genotype is still a controversial issue, because much scientific evidence suggests that APOE ε4 works as a pro-inflammatory that induces the production of inflammatory biomarkers via several mechanisms [22-29]. Concomitantly, in the scientific literature, there are a few studies that suggest the benefits arising from the having a copy of APOE ε4 because it works as an anti-inflammatory [30, 31].

In the current study, the Cache County Memory Study (CCMS) was used to examine the influence of APOE-epsilon genotypes and SNPs in 20 genes previously associated with AD with plasma CRP levels. The hypotheses of this study are divided into primary hypotheses and exploratory hypotheses (Table 5.1). Primary hypotheses,

which are based on previously published reports, include genes that are associated with either increased or decreased levels of inflammatory biomarkers. Exploratory hypotheses included genes that are associated with Alzheimer's disease, but not known to be associated with inflammation.

Materials and Methods

Study participants

This investigation used data from the Cache County Memory Study, a prospective cohort study among elderly who were 65 years old and older at the baseline in 1995 and who were permanent residents of Cache County, Utah. This population is largely non-Hispanic White (5,092 residents), and the genetic makeup is mostly from Northern European ancestry. The institutional review boards of each collaborating site at Utah State University, Duke University Medical Center, and The Johns Hopkins University approved the protocol of the study. Participants were interviewed about demographic characteristics, health history, and family history of dementia, use of medications, alcohol, tobacco, other lifestyle factors, and extensive cognitive testing. Re-examination of the study participants was completed three more times in subsequent years. Details of the study protocols have been previously published [32].

CRP assessment

In 2002, fasting blood samples were obtained and assayed for CRP from 2185 participants in Wave 3 at McKay Dee Laboratory Hospital, Ogden, UT. Dade's nephelometry method has been considered for quite some time as a gold standard for these tests in the laboratory industry [33]. Many large reference studies refer to the Dade

BNII assay that uses particle enhanced immunonephelometry to detect high-sensitivity CRP (hs-CRP). Dade was one of the first vendors to receive FDA approval for cardiac marker claims for their sensitive CRP assay [34, 35]. Typically, expected values for healthy individuals are found to be less than 3.00 mg/L, or 0.3 mg/dL [36]. The measuring range is determined by the lower limit of the reference curve and depends on the concentration of the standard used. The typical limit of detection for the method was 0.175 mg/L or 0.0175 mg/dL. The upper level of detection was typically 1150mg/L or 150 mg/dL. We defined elevated CRP as values >3.0 mg/L [34].

Genotyping

At the baseline of the CCMS, DNA buccal samples were obtained from 4,654 participants to genotype APOE at Duke University School of Medicine. Later, a mixture of 2,974 DNA buccal and blood samples were genotyped for 20 non-APOE LOAD risk alleles at Brigham Young University by Dr. Kauwe using custom TaqMan assays [37, 38]. The genotype assays included BIN1, CLU, CD33, PICALM, MS4A6A, MS4A4E, CD2AP, APOE, ABCA7, AGTR1, DTNA, HTR2C, MMP8, MPP7, EPHI1, SORCS1, TOMM40, PPP3R1, CR1, and MAPT/STH.

Statistical Analyses

Descriptive analyses were conducted to examine the association between CRP and other factors, such as gender (male, female), age (years), body mass index (BMI weight in kilograms/ height in meters^2), educational level (less than high school, and more than high school), drinking and smoking habits (never, former, current); health variables included diabetes (no, yes), stroke (no, yes), and heart attack (no, yes), APOE genotype (no e4, 1 or 2 e4), and cholesterol (mg, continues).

The epsilon polymorphism in the APOE gene was defined by six- levels (ε3/ ε2, ε2/ ε3, ε2/ ε4, ε3/ ε3, ε3/ ε4, and, ε4/ ε4). Chi-square analyses of contingency tables of CRP levels (low:< 3.00 mg/L, high:> 3.0 mg/L) by genotype categories were performed to evaluate associations. Analysis of Variance (ANOVA) was used to test for differences between the mean of CRP across levels of genotypes. We also tested the associations between APOE- epsilon genotypes and APOE rs439401, TOMM40 rs1160985.

AD-related genotypes define three-level categorical variables (major allele homozygote, heterozygote, minor allele homozygote). The three-level genotype variables were used in additive genetic models to test for an effect of 0, 1, or 2 alleles. Analysis of Variance (ANOVA) was used to test for differences between the mean of CRP across levels of genotypes. Potential confounding variables including BMI, smoking, age, diabetes, stroke, heart attack, and gender were evaluated. Logistic regression models were used to estimate the risk of CRP elevation (> 3.0 mg/L) by genotype level. The major allele homozygote was used as a reference in these models to estimate the odds ratio (ORs) and 95% confident intervals (CIs) for CRP elevation (coded 0, 1). All tests were performed first with gender as covariates, and then models were stratified by gender. This stratification provides a means of comparing CRP- genotype association between males and females [39], thus making it possible to observe the differences. Participants with dementia (n= 154) were excluded from all analysis. Statistical analyses were conducted using SPSS, version 22.

Results

Baseline demographic characteristics of the study participants are shown in Table 5.2. Participants with a high level of CRP were more likely to be women, less educated

and had higher BMI. High CRP levels were also associated with current smoking. Those in the higher vs. lower CRP level reported more strokes (10.1 vs. 7.3 percent) and the prevalence of diabetes was slightly higher in the high CRP group.

The genotype distribution of the APOE-epsilon genotypes and the mean plasma CRP level for APOE-epsilon genotype and the percent of normal and elevated CRP by genotype group are presented in Table 5.3. A Chi-square test for association between APOE-epsilon genotypes and CRP levels revealed that mean CRP level was significantly different between APOE-epsilon genotypes (p= <0.001). Lower mean CRP was observed among APOE-epsilon genotype ε2/ ε2 and ε4/ε4, and the highest mean CRP was observed among ε2/ ε4 allele genotype.

A Chi-square test for association was conducted between APOE-epsilon genotypes and APOE and TOMM40 polymorphisms. There was a statistically significant association between gene APOE-epsilon genotypes and APOE rs439401, TOMM40 rs157580, and TOMM40 rs157580, (χ^2 (5) = 33.8, p = <0.001), (χ^2 (10) = 400, p = <0.001), and (χ^2 (10) = 454, p = <0.001), respectively (Table 5.4).

The genotype distribution of AD-related genes appears in Table 5.5. Mean plasma of CRP by the AD-related genotypes are presented in Table 5.6. Mean CRP levels were significantly different between APOE rs439401 and TOMM40 rs157580 genotypes ($P=$ <0.001, $P=$ <0.001, $P=$ 0.002), respectively. Higher mean plasma CRP concentrations were found in the minor allele heterozygotes and homozygotes compared to the major allele homozygotes for both APOE and TOMM40.

The results of the logistic regression models that estimated the relative risk of having an elevated plasma CRP are shown in Table 5.7. The models presented were

adjusted for gender, age, education, BMI, smoking, alcohol intake, diabetes, stroke, myocardial infarction. The adjusted multivariate logistic analysis of 20 AD-related genes found that individuals compared to major allele as the reference category had increased the risk of elevated CRP level for minor allele homozygotes; adjusted OR (aOR) and 95% confidence intervals (CIs)); APOE rs439401(aOR = 1.4 [95%CI 1.1- 1.7]), TOMM40 rs157580 (aOR= 1.2 [95%CI 0.96- 1.46]). In contrast, individuals compared to major allele homozygote as the reference category had decreased the risk of elevated CRP levels for minor allele homozygotes MMP8 rs1892886 (aOR = 0.78 [95%CI 0.64- 0.9]). No associations between others genes and CRP elevation were observed levels was observed.

When the data were stratified by gender, we found that mean CRP levels were strongly associated with APOE-epsilon genotype in both. Lower mean plasma CRP concentrations were found in major allele homozygotes compared to minor allele heterozygotes and homozygotes in SNPs APOE rs439401 in both men and women. TOMM40 rs157580 genotype was associated with CRP in males but not in females. Higher mean plasma CRP concentration was found in the major allele homozygote compared to minor allele heterozygotes and homozygotes in MMP8 and HTR2C for males and MS4A6A in females (Table 5.9 and Table 5.10).

The results of the logistic regression analyses for the relative risk of having an elevated plasma CRP stratified by gender are shown in Table 5.11. The adjusted multivariate logistic analysis of 20 AD-related genes found that individuals compared to major allele homozygotes as the reference category, increased risk of elevated CRP level for minor allele homozygotes for males were: APOE rs439401(aOR = 1.6 [95%CI 1.1-

2.1]) and TOMM40 rs157580 (aOR= 1.5 [95%CI 1.07- 2.1]). Decreased risk of elevated CRP for minor allele homozygotes in males was found for MMP8 rs1892886 (aOR = 0.64 [95%CI 0.46- 0.89]), CR1 rs665401 (aOR = 0.59 [95%CI 0.42- 0.84]), CR1 rs3818361 (aOR = 0.43 [95%CI 0.28- 0.66]), and CR1 rs4844609 (aOR = 0.38 [95%CI 0.19- 0.80]). These associations were not observed in women.

While the associations between AD-related genes and risk of elevated CRP appeared to be present only in men and not among women, there was not a significant multiplicative interaction between most AD-related genes and CRP elevation (p > 0.05). Only TOMM40 rs157580, CR1 rs665401, CR1 rs3818361, and CR1 rs4844609 were significant with the multiplicative interaction between most AD-related genes and CRP elevation (p= 0.0418, 0.005, 0.002, 0.0193), respectively.

Discussion

The present study found that APOE-epsilon genotypes influence the risk of systemic inflammation but in an unexpected direction the ε4/ε4 genotype, associated with the highest risk of AD, had among the lowest mean CRP compared to other APOE genotype. Plasma CRP differed in a similar pattern across APOE-epsilon genotypes in both genders. When major allele homozygotes were compared to minor allele homozygotes, the risk of elevation CRP increased in those who have APOE rs439401 and TOMM40 rs157580. In contrast, the risks of elevation CRP decrease in those who have minor allele homozygotes MMP8 rs1892886, CR1 rs665401, CR1 rs3818361, and CR1 rs4844609. These associations were found to be stronger in men vs. women.

Several prospective studies have demonstrated that CRP is an independent predictor of future risk for AD, and it may aid in identifying subjects at high risk [6-9, 40]. The

observation of elevated CRP in subjects with AD has led to extensive studies on the role of inflammatory reactions in the pathogenesis of AD [9, 10, 41].

The link between plasma CRP and the common allelic variants ε2, ε3, and ε4 of the APOE gene has been observed in some earlier studies. Five studies of APOE [34, 99-102] showed that APOE-epsilon genotypes had no effect on inflammatory biomarkers. Other studies were consistent with our current results. Angelopoulos et al., and Haan et al., examined the association between APOE ε3/ε4 in healthy elderly Latinos. They found that ε3/ε4 reduced CRP levels among participants [42, 43]. In Japanese Americans, CRP levels were found to be low in ε4/ε4 and ε3/ε4 participants, but not with ε/ε2 genotype [44]. Moreover, a data from the Czech part of the HAPIEE (Health, Alcohol, and Psychosocial factors In Eastern Europe) study reported that ε3/ε4 and ε4/ε4 was associated with reduced CRP levels among 2,886 males and 3,344 females [45]. This pattern of association is consistent with other studies that indicated ε4 carriers have lower levels of plasma CRP in the elderly and different patient groups [29, 46-52]. APOE ε4 were associated with higher CRP levels, the sensitive inflammatory biomarker and predictor of Alzheimer disease [53], only one study of young participants stratified by gender and they found that APOE ε4 was associated with lower mean CRP, but only for men not for women [54].

The present result that is consistent with the most previously published studies highlighted the contradiction regarding the relationship between APOE genotypes, CRP, and AD. Until now the mechanism has been unknown for how APOE isoforms affect inflammation and risk of AD but it has been suggested that each APOE isoform has been implicated in different modulation mechanisms in regards to inflammatory responses

(apoE2 > apoE3 > apoE4) [55]. Some studies suggest anti-inflammatory benefits arising from having genotypes of APOE ε2/ ε3 [24, 56-61], ε3/ ε4 [43, 62], ε4 [29, 46-52], ε4/ ε4 [19, 29, 49-52, 63-66] which suggest that this association may be influenced by different independent mechanism. Other studies suggest the pro-inflammatory effect of APOE ε4 [22-28]. Over the last decades, high level of CRP has been used widely to estimate the risk of several chronic diseases including cancer [67], type 2 diabetes [68], coronary artery disease risk, damage from a heart attack [69], inflammatory bowel disease [70], some forms of arthritis [71], pelvic inflammatory disease [72], lupus [71], and AD [73]. Moreover, individuals with APOE ε4 genotype are at increased risk of cardiovascular disease, end stage renal disease [74], and AD [75]. Genetic data also revealed that high levels of CRP are related to gene polymorphisms by increasing the risk of some disease such as cardiovascular disease rather than inflammatory status, which may explain the limited effects of the environmental factors [45, 76]. Thus, further experimental studies are needed to explain this conflict evidence that came from only observational studies.

No previous study, to our knowledge, has examined associations between rs439401 in APOE and rs157580 in TOMM40 with inflammatory biomarkers in males. On the other hand, The Women's Health Initiative (WHI) study of 8,280 African American reported [77] and 7,570 African Americans (AA) from the Candidate Gene Association Resource (CARe) study [78] reported that CRP is significantly associated with APOE rs157580 and TOMM40 rs439401 loci. The biologic mechanism of the relationship between these polymorphisms and CRP is not clear [45]. Both TOMM40 and APOE are located on chromosome 19 [79]. AD pathology in multiple brain regions have been associated with SNPs in APOE and TOMM40 genes [80]. Even though the effect of

length variation between TOMM40 and APOE has been reported [79, 81], there are no studies conducted, to our knowledge, that have analyzed the interaction effect of rs157580 and rs439401 polymorphisms on CRP levels, thus more studies are needed to explore and explain the effect of the interaction between APOE rs157580 and TOMM40 rs439401 on CRP levels as a dependent variable, particularly among elderly.

No previous study, to our knowledge, has examined associations between rs6656401, rs3818361, and rs4844609 in CR1, rs1892886 in MMP8, and CRP levels in men. The mechanisms underlying inflammation and the immunological network leading to AD are not well known. Genes including BIN1 [82, 83], and AGTR1 [84] have been linked to inflammation as both pro-inflammatory and anti-inflammatory. In the scientific literature, there are a few studies that reported BIN1 [85-90] and CLU [91-94] as anti-inflammatory. Other evidence suggests that CD2AP [95-98], AGTR1 [99-101], MMP8 [102-106], MMP7 [107-111], TOMM40 [28, 112], CR1 , CD33 [113], and MS4A6A [113] work as a pro-inflammatory that induces the production of inflammatory biomarkers via several mechanisms. Three studies of CLU studies [114-116] reported that these genes have no effect on inflammatory biomarkers.

To our knowledge, this is the first study that explores the multiplicative interaction between AD-related genes and the risk of elevated CRP. Thus, further studies are needed to confirm our results.

 Our study has several key strengths, including a large sample size for determining the association between APOE-epsilon genotypes and 20 Alzheimer's Disease-related genes and CRP levels in both males and females. Participants in our sample were Caucasians, and populations with other genetic background may have different

associations. The results of our analysis must be considered in light of its limitations. CRP is a single measure of systemic inflammation that is a complex process, and further studies of additional inflammatory biomarkers would be useful [117].

In conclusion, our finding supports the hypothesis that among Caucasian males, the presence of minor alleles of APOE (C/C) rs439401 and TOMM40 (A/A) rs157580 may be a risk factor to increase inflammation in elderly. Conversely, the minor allele of MMP8 (T/T) rs1892886, CR1 (G/G) rs6656401, CR1 (A/A) rs3818361, and CR1 (A/A) rs4844609 is associated with decreased risk of CRP elevation in Caucasian males. More mechanistic studies or using other inflammatory biomarkers are needed to show how genetic polymorphisms affect systemic inflammation, which has long term effects on the development of Alzheimer's.

Table 5.1: Studies reporting on the relationship between Alzheimer's- associated genes and inflammatory biomarkers.

Genes	Inflammatory type	Published evidence between AD genes and inflammatory biomarkers[1]	
		Statistically significant p-value <0.05	Statistically Not significant p-value >0.05
Primary hypotheses[2]:			
APOE[1]	Pro-inflammatory ε4/ ε4	[22-28]	[40, 118-121]
	Anti-inflammatory ε2, ε3	[24, 56-61]	
	Anti-inflammatory ε3/ ε4	[43, 62]	
	Anti-inflammatory ε4	[29, 46-52]	
	Anti-inflammatory ε4/ ε4	[29, 49-52, 63-65]	
BIN1[1]	Pro-inflammatory	No references found related to pro-inflammation	---------------------------
	Anti-inflammatory	[85-90]	---------------------------
CLU[1]	Pro-inflammatory	No references found related to anti-inflammation	[114-116]
	Anti-inflammatory	[91-94]	
CD2AP[1]	Pro-inflammatory	[95-98]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
AGTR1[1]	Pro-inflammatory	[99-101]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
MMP8[1]	Pro-inflammatory	[103-106]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
MPP7[1]	Pro-inflammatory	[102, 107-111]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
TOMM40[1]	Pro-inflammatory	[28, 112]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
CR1[1]	Pro-inflammatory	[122-124]	---------------------------
	Anti-inflammatory	No references found related to anti-inflammation	

Exploratory hypotheses[3]:			
CD33[2]	Pro-inflammatory	[113]	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
PICALM[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
MS4A6A[2]	Pro-inflammatory	[113]	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	-------------------------
MS4A4E[2]	Pro-inflammatory	No references found related to pro-inflammation	
	Anti-inflammatory	No references found related to anti-inflammation	
ABCA7[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
DTNA[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
HTR2C[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
EPHI1[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
SORCS1[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
PPP3R1[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	
MAPT/STH[2]	Pro-inflammatory	No references found related to pro-inflammation	-------------------------
	Anti-inflammatory	No references found related to anti-inflammation	

[1] Note: Studies were identified in PubMed and Scopus using the following combinations of search terms: ("SNPs number" or " gene names") and ("genotype" or "gene" or "polymorphisms") and ("crp" or "c-reactive protein").

[2] Genes hypothesized to be associated with systemic inflammation based on literature review.

[3] Genes without strong evidence of association with systemic inflammation.

Table 5.2: Demographic characteristics by levels of C- reactive protein (CRP) in the Cache County Study on Memory, Health and Aging in Wave 3 (N= 2031).

Characteristic	Levels of plasma CRP concentration (mg/L)		p-value[1]
	<3.0 (mg/L)	>3.0 (mg/L)	
Gender			
- Male (%)	63.5	36.5	<0.001
- Female (%)	54.9	45.1	
Less than high school education (%)	54.9	61.8	0.002
More than high school education (%)	45.1	38.2	
Age in years (SD)[2]	73.0± 5.4	73.1± 5.5	0.480
Body mass index (kg/m^2) (SD)[2]	25.9± 4.0	27.2± 4.4	<0.001
Current smoke (%)[3]	1.4	2.9	0.042
Current alcohol (%)[3]	4.4	3.7	0.442
At least one APOE e4 allele (%)	35.8	26.2	<0.001
Diagnosed with diabetes (%)	17.4	20.0	0.078
Diagnosed with stroke (%)	7.3	10.1	0.018
Diagnosed with heart attack (%)	14.4	16.0	0.178

[1] p-values were obtained by using the Chi-square test for CRP (low vs. high) for categorical variables and Analysis of Variance (ANOVA) for continuous variables.

[2] Means± standard deviation (SD).

[3] A current smoker was defined as a subject who reported currently smoking; a current drinker was defined as a subject who reported currently drinking alcohol.

Table 5.3: Genotype distributions and mean levels of C-reactive protein (CRP) by APOE polymorphisms genotypes and CRP Levels in the Cache County Memory Study (CCMS).

Gene ID	Genotype[1]	%	CRP levels		p-value[2]	Mean CRP[3]	p-value[4]
			<3.0 (mg/L)	≥3.0 (mg/L)			
			n (%)	n (%)			
Epsilon	ε2/ ε2	0.7	9 (64.3)	5 (35.7)	<0.001	2.8± 2.61	<0.001
	ε2/ ε3	14.4	135 (46.2)	157 (53.8)		5.6± 8.2	
	ε2/ ε4	4.2	54 (63.5)	31 (36.5)		6.4± 13.0	
	ε3/ ε3	52.7	615 (57.6)	453 (42.4)		4.6± 7.3	
	ε3/ ε4	25.5	335 (64.8)	182 (35.2)		3.8± 6.3	
	ε4/ ε4	2.4	37 (75.5)	12 (24.5)		3.0± 6.6	

[1] APOE-epsilon genotypes defined by variants in APOE SNPs rs429358 and rs7412.

[2] p-values were obtained by using the chi-square test for CRP (low vs. high) for categorical variables.

[3] Means± standard deviation (SD).

[4] p-values were obtained by using Analysis of Variance (ANOVA).

Table 5.4: Cross-tabulations of APOE-epsilon genotype and APOE and TOMM40 polymorphisms in the Cache County Memory Study (CCMS).

Gene ID	Genotype	APOE rs4394011			p-value[2]	TOMM40 rs1160985			p-value[2]	TOMM40 rs157580			p-value[2]
		R/R[1]	C/R[1]	C/C[1]		R/R[2]	C/R[2]	C/C[2]		R/R[2]	C/R[2]	C/C[2]	
		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Epsilon	ε2/ ε2	0.8	0.0	0.0	<0.001	0.4	0.4	0.1	<0.001	0.1	0.3	0.3	<0.001
	ε2/ ε3	7.1	6.1	0.2		4.5	6.2	3.2		3.3	6.1	3.8	
	ε2/ ε4	3.2	0.3	0.0		2.0	1.4	0.0		1.3	2.1	0.2	
	ε3/ ε3	15.1	26.5	14.5		14.2	26.9	13.7		16.8	27.0	12.3	
	ε3/ ε4	12.4	10.7	0.7		11.8	12.1	0.6		12.8	10.6	0.8	
	ε4/ ε4	2.2	0.1	0.0		2.4	0.1	0.0		2.1	0.1	0.0	

[1] R is the major allele and C is the minor allele.
[2] p-values were obtained by using the chi-square test for APOE-epsilon genotype and AD-related genes.

Table 5.5: Genotype distributions of the Alzheimer's associated genes in the Cache County Memory Study (CCMS).

Gene ID	SNP	Full name gene	n	Elevated CRP (≥ 3.0) by genotype		
				R/R[1] %	C/R[1] %	C/C[1] %
APOE	rs439401	Apolipoprotein	1938	35.4	50.1	14.5
BIN1	rs744353	Bridging integrator 1	1810	50.2	40.3	9.5
CLU	rs11136000	Clusterin	1959	37.2	48.8	13.9
CD2AP	rs9349407	CD2-associated protein	1975	53.1	39.1	7.8
AGTR1	rs2131127	Angiotensin II receptor, type 1	1931	42.5	44.8	12.7
MMP8	rs1892886	Matrix metallopeptidase 8	1913	56.9	36.6	6.4
MPP7	rs1457177	Membrane protein, palmitoylated 7	1961	85.2	14.4	0.4
TOMM40	rs1160985	Translocase of outer mitochondrial membrane 40 homolog	1782	33.7	50.2	16.1
	rs157580		1959	32.1	49.8	18.0
CR1	rs6656401	Complement receptor 1	1974	68.4	28.8	2.7
	rs3818361		1331	67.3	29.5	3.1
	rs4844609		1956	95.0	4.8	0.2
CD33	rs3865444	Siglec-3	1981	44.1	43.5	12.3
PICALM	rs3851179	Phosphatidylinositol Binding Clathrin Assembly Protein	1979	38.3	46.9	15
MS4A6A	rs610932	Membrane-spanning 4-domains, subfamily A, member 6A/	1936	33.5	47	19.5
MS4A4E	rs670139	Membrane-spanning 4-domains, subfamily A, member 4E	1580	35.9	47.9	16.1
ABCA7	rs3752246	ATP-binding cassette, sub-family A (ABC1),	1976	66.3	30.3	3.4
DTNA	rs4458079	Dystrobrevin, alpha	1963	78.7	19.2	2.1
HTR2C	rs6318	5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled	1962	74.7	16.5	8.8
EPHA1	rs11767557	EPH receptor A1	1967	65.4	30.2	4.4

SORCS1	rs7093634	Sortilin-related VPS10 domain containing receptor 1	1854	38.0	49.2	12.7
PPP3R1	rs1868402	Protein phosphatase 3, regulatory subunit B, and alpha	1961	48.9	41.8	9.3
MAPT/STH	rs3785883	Microtubule-associated protein tau and saitohin	1966	67.6	28.9	3.5

[1] R is the major allele and C is the minor allele.

Table 5.6: Mean levels of C-reactive protein (CRP) by genotype of Alzheimer's associated genes in the Cache County Memory Study.

Gene ID	SNP	Mean CRP[1]			p-value[3]
		R/R[2]	C/R[2]	C/C[2]	
Primary hypotheses					
APOE	rs439401	4.3± 7.6	4.8± 7.6	4.9± 7.8	<0.001
BIN1	rs744353	4.6± 7.7	4.6 ± 7.8	4.1± 8.4	0.750
CLU	rs11136000	4.3± 6.4	4.7± 8.2	5.0± 7.53	0.492
CD2AP	rs9349407	4.4± 7.0	4.9± 8.4	4.5± 7.2	0.890
AGTR1	rs2131127	4.7± 7.8	4.5± 7.3	4.7± 8.6	0.448
MMP8	rs1892886	4.9± 7.6	4.3± 7.3	4.3 ± 9.9	0.078
MPP7	rs1457177	4.7± 7.8	4.3± 7.0	2.5± 2.3	0.238
TOMM40	rs1160985	4.0± 4.9	4.8± 8.4	4.6± 7.7	0.868
TOMM40	rs157580	3.9± 6.1	5.1± 8.7	4.8± 7.1	0.002
CR1	rs6656401	4.7± 7.8	4.6± 7.4	4.1± 6.7	0.682
CR1	rs3818361	4.9± 7.7	4.8± 7.3	4.3± 7.2	0.670
CR1	rs4844609	5.0± 2.5	3.7± 5.8	4.6± 7.7	0.155
Exploratory hypotheses					
CD33	rs3865444	5.0± 8.9	4.2± 5.9	5.1± 8.0	0.642
PICALM	rs3851179	4.7± 8.3	4.8± 8.3	4.8± 4.8	0.967
MS4A6A	rs610932	4.3± 7.1	4.8± 8.1	4.8± 7.7	0.107
MS4A4E	rs670139	4.6± 7.0	4.7± 8.5	4.1± 6.1	0.176
ABCA7	rs3752246	4.6± 7.6	4.5± 7.5	4.6± 6.4	0.834
DTNA	rs4458079	4.6± 7.3	4.8± 9.1	4.7± 4.7	0.493
HTR2C	rs6318	4.5± 7.1	4.9± 8.9	4.5± 8.1	0.222

EPHA1	rs11767557	4.6± 7.5	4.8± 8.2	.3.3± 3.1	0.532
SORCS1	rs7093634	4.4± 6.9	4.9± 8.1	4.2± 8.5	0.170
PPP3R1	rs1868402	4.4± 6.7	4.9± 8.8	4.9± 7.2	0.828
MAPT/STH	rs3785883	5.1± 6.5	4.1± 5.5	4.8± 8.5	0.467

[1] Means± standard deviation (SD).
[2] R is the major allele and C is the minor allele.
[3] P values were obtained by using Analysis of Variance (ANOVA).

Table 5.7: Estimated effects of Alzheimer's associated genes of plasma biomarker concentration C-reactive protein (CRP) levels (high vs. low) from conditional logistic regression in the Cache County Memory Study.

Genes	SNP	Genotype			p- value[2]
		R/R[1]	C/R[1]	C/C[1]	
APOE	rs439401	1.00 [reference]	1.3 (1.01- 1.8)	1.4 (1.1- 1.7)	0.004
BIN1	rs744353	1.00 [reference]	1.06 (0.746- 1.5)	1.06 (0.869- 1.3)	0.552
CLU	rs11136000	1.00 [reference]	0.99 (0.73- 1.3)	0.87 (0.71- 1.0)	0.584
CD2AP	rs9349407	1.00 [reference]	0.93 (0.65- 1.3)	0.98 (0.80- 1.1)	0.717
AGTR1	rs2131127	1.00 [reference]	1.2 (0.89- 1.6)	1.10 (0.90- 1.3)	0.199
MMP8	rs1892886	1.00 [reference]	0.77 (0.52- 1.1)	0.78 (0.64- 0.9)	0.020
MPP7	rs1457177	1.00 [reference]	0.63 (0.15- 2.5)	0.93 (0.71- 1.2)	0.473
TOMM40	rs1160985	1.00 [reference]	0.96 (0.71- 1.3)	0.95 (0.78- 1.2)	0.813
TOMM40	rs157580	1.00 [reference]	1.5 (1.10- 1.9)	1.2 (0.96- 1.46)	0.008
CR1	rs6656401	1.00 [reference]	0.82(.475- 1.4)	0.89 (.73- 1.1)	0.224
CR1	rs3818361	1.00 [reference]	0.89 (0.47- 1.7)	0.81 (0.63- 1.04)	0.152
CR1	rs4844609	1.00 [reference]	No observation	0.80 (0.53-1.2)	0.616
CD33	rs3865444	1.00 [reference]	0.98 (0.72- 1.3)	0.96 (0.79- 1.1)	0.802
PICALM	rs3851179	1.00 [reference]	1.03 (0.773- 1.3)	1.00 (0.819- 1.2)	0.861
MS4A6A	rs610932	1.00 [reference]	1.09 (0.833- 1.4)	1.03 (0.834- 1.2)	0.537

Gene	SNP				p
MS4A4E	rs670139	1.00 [reference]	0.89 (0.65- 1.2)	0.94 (0.75-1.1)	0.451
ABCA7	rs3752246	1.00 [reference]	0.88 (0.53- 1.4)	1.05 (0.86-1.2)	0.919
DTNA	rs4458079	1.00 [reference]	1.6 (0.81- 3.5)	0.92 (0.73-1.1)	0.858
HTR2C	rs6318	1.00 [reference]	1.09 (0.781-1.5)	0.95 (0.72-1.2)	0.793
EPHA1	rs11767557	1.00 [reference]	0.96 (0.60- 1.5)	0.87 (0.71-1.0)	0.322
SORCS1	rs7093634	1.00 [reference]	1.07 (0.790-1.4)	1.12 (0.911-1.3)	0.426
PPP3R1	rs1868402	1.00 [reference]	1.3 (0.927- 1.8)	1.1 (0.925-1.3)	0.081
MAPT/STH	rs3785883	1.00 [reference]	1.1 (0.64- 1.9)	1.0 (0.821-1.2)	0.779

[1] R is the major allele and C is the minor allele.

[2] Values are 95% Confidence Interval in parentheses (all such values). Adjusted variables in multivariate models included body mass index (kg/m2, continuous), smoking (never, former, current), Age, in years (65-74, 75-84, 85+), diabetes (No, Yes), Stroke (No, Yes), Heart attack (yes or no), cholesterol (mg, continues), and gender (male, female).

Table 5.8: Demographic Characteristics by C- reactive protein (CRP) and stratified by gender in the Cache County Study on Memory, Health and Aging in Wave 3.

Characteristic	Plasma CRP concentration (mg/L) n%					
	Male (n= 840)			Female (n= 1191)		
	<3.0 (mg/L)	≥3.0 (mg/L)	p-value[1]	<3.0 (mg/L)	≥3.0 (mg/L)	p-value[1]
Less than high school (%)	33.5	66.5	0.026	52.5	47.5	0.001
More than high school (%)	40.5	59.5		57.1	42.9	
Age in years (SD)[2]	72.1± 5.0	73.3± 5.6	0.033	73.5± 5.8	72.8± 5.4	0.002
Body mass index (kg/m^2) (SD)[2]	26.0± 3.7	26.7± 4.0	0.017	24.4± 4.5	26.6± 5.2	0.000
Current smoke (%)[3]	1.9	5.4	0.002	0.9	1.5	0.580
Current alcohol (%)[3]	6.6	5.4	0.95	2.7	2.7	0.883
At least one APOE e4 allele (%)	36.6	23.7	0.000	35.1	27.7	0.004
Diagnosed with diabetes (%)	19.7	20.7	0.420	15.6	19.7	0.036
Diagnosed with stroke (%)	7.3	8.8	0.261	7.3	10.8	0.024
Diagnosed with heart attack (%)	17.1	23.1	0.021	12.2	11.9	0.470

[1] P values were obtained by using the chi-square test for CRP (low vs. high) for categorical variables and Spearman rank correlation for continues variables.
[2] Means ± standard deviation (SD).

[3] A current smoker was defined as a subject who reported currently smoking; a current drinker was defined as a subject who reported currently drinking alcohol.

Table 5.9: Mean levels of C-reactive protein (CRP) by genotype of APOE gene stratified by gender in the Cache County Memory Study.

Gene ID	SNPs	N	Male		N	Female	
			Mean CRP[1] (mg/L)	p-value[2]		Mean CRP[1] (mg/L)	p-value[2]
Epsilon	ε2/ ε2	2	1.7± 0.63	<0.001	12	3.0± 2.7	0.006
	ε2/ ε3	134	5.5± 8.7		158	5.7± 7.8	
	ε2/ ε4	32	5.7± 14.5		53	6.9± 12.2	
	ε3/ ε3	435	4.2± 6.9		633	4.9± 7.6	
	ε3/ ε4	210	3.6± 6.3		307	4.0± 6.3	
	ε4/ ε4	25	1.6± 1.2		24	4.4± 9.3	

[1] Means± standard deviation (SD).
[2] P values were obtained by using Analysis of Variance (ANOVA).

Table 5.10: Mean levels of C-reactive protein (CRP) by genotype of Alzheimer's associated genes stratified by gender in the Cache County Memory Study.

Genes	SNP	Mean CRP[1]			p-value[3]	Mean CRP[1]			p-value[3]
		Male				Female			
		R/R[2]	C/R[2]	C/C[2]		R/R[2]	C/R[2]	C/C[2]	
Primary hypotheses									
APOE	rs439401	3.9± 7.7	4.3± 6.8	5.1± 8.9	0.003	4.5± 7.6	5.2± 8.1	4.8± 6.9	0.040
BIN1	rs744353	3.8± 4.9	4.4± 9.3	4.8± 10.4	0.547	5.8± 9.1	5.4± 8.7	4.4± 6.7	0.292
CLU	rs11136000	3.6± 4.6	4.2± 8.2	5.0± 11.4	0.921	5.1± 6.9	4.9± 8.2	4.7± 7.2	0.423
CD2AP	rs9349407	3.7± 5.3	5.4± 12.2	5.3± 11.9	0.787	5.0± 7.8	4.9± 7.8	4.5± 5.5	0.956
AGTR1	rs2131127	4.4± 8.3	4.8± 11.2	3.5± 3.6	0.549	4.9± 7.2	4.8± 7.3	5.2± 10.2	0.823
MMP8	rs1892886	5.1± 9.3	4.1± 10.2	2.6± 3.3	0.005	5.4± 12.5	4.6± 7.4	5.0± 7.0	0.926
MPP7	rs1457177	4.6± 9.9	3.8± 4.9	2.4± 1.9	0.949	5.0± 7.7	4.4± 7.2	2.7± 2.6	0.069
TOMM40	rs1160985	4.2± 8.2	4.7± 10.6	4.2± 8.4	0.642	4.4± 4.8	5.0± 8.6	4.9± 7.4	0.997
TOMM40	rs157580	3.7± 7.5	4.9± 10.6	5.1± 9.4	0.011	4.1± 5.2	5.5± 9.5	4.6± 5.2	0.153
CR1	rs6656401	4.6± 9.6	4.3± 8.7	4.1± 8.5	0.242	5.0± 8.4	4.6± 6.0	4.1± 4.2	0.765
CR1	rs3818361	4.7± 8.1	4.9± 12.7	4.6± 9.9	0.221	5.1± 8.3	5.0± 6.5	4.1± 4.5	0.638
CR1	rs4844609	4.5± 9.3	4.6± 9.4	3.4± 7.2	0.105	6.2± 1.9	3.9± 4.2	4.9± 7.8	0.545
Exploratory hypotheses									
CD33	rs3865444	5.1± 11.8	4.0± 6.6	4.2± 8.1	0.720	5.2± 8.7	4.4± 6.5	5.3± 7.2	0.220
PICALM	rs3851179	3.5± 5.7	4.3± 7.6	5.1± 12.0	0.424	4.2± 4.2	4.9± 7.1	5.0± 9.1	0.919
MS4A6A	rs610932	5.9± 14.8	4.1± 7.2	4.3± 7.8	0.397	4.8± 5.9	5.3± 8.4	4.5± 7.4	0.014
MS4A4E	rs670139	4.4± 6.8	4.2± 8.5	5.1± 11.9	0.151	4.6± 8.4	5.0± 8.2	4.7± 6.5	0.106
ABCA7	rs3752246	5.0± 7.6	3.9± 7.7	4.7± 9.9	0.645	4.3± 5.1	5.0± 7.7	4.8± 7.7	0.313
DTNA	rs4458079	4.4± 8.4	4.9± 12.4	5.9± 4.4	0.232	4.8± 6.9	5.4± 10.3	4.3± 5.1	0.818

HTR2C	rs6318	4.7± 8.8	0.38± 0.13	4.0± 6.7	0.002	3.9± 4.3	4.0± 9.0	4.9± 7.4	0.691
EPHA1	rs11767557	5.0± 11.0	3.8± 5.2	2.5± 2.5	0.133	4.5± 5.9	5.7± 10.4	3.7± 3.3	0.833
SORCS1	rs7093634	3.4± 6.3	4.8± 8.9	4.6± 10.9	0.262	5.5± 11.7	5.0± 7.4	4.6± 6.5	0.424
PPP3R1	rs1868402	4.8± 8.2	4.9± 10.0	4.2± 9.0	0.956	5.0± 6.3	5.0± 8.3	4.8± 7.3	0.895
MAPT/STH	rs3785883	4.6± 9.3	4.4± 10.3	3.9± 5.9	0.969	5.1± 8.5	4.2± 5.0	5.8± 6.6	0.344

[1] Means± standard deviation (SD).
[2] R is the major allele and C is the minor allele.
[3] P values were obtained by using Analysis of Variance (ANOVA).

Table 5.11: Estimated effects of Alzheimer's associated genes on plasma biomarker concentration C-reactive protein (CRP) levels (high vs. low) from conditional logistic regression stratified by gender in the Cache County Memory Study.

Genes	SNP	Male				Female			
		R/R[1]	C/R[1]	C/C[1]	p- value[2]	R/R[1]	C/R[1]	C/C[1]	p- value[2]
APOE	rs439401	1.00 [reference]	1.9 (1.2- 3.1)	1.6 (1.1- 2.1)	0.001	1.00 [reference]	1.0 (0.74- 1.6)	1.3 (1.00- 1.7)	0.259
BIN1	rs744353	1.00 [reference]	1.2 (0.71- 2.3)	1.1 (0.80- 1.5)	0.337	1.00 [reference]	0.99 (0.63- 1.5)	1.07 (0.82- 1.4)	0.791
CLU	rs11136000	1.00 [reference]	0.95 (0.58- 1.5)	0.87 (0.63- 1.2)	0.658	1.00 [reference]	1.01 (0.68- 1.5)	0.86 (0.66- 1.1)	0.717
CD2AP	rs9349407	1.00 [reference]	0.82 (0.46- 1.4)	0.84 (0.62- 1.1)	0.281	1.00 [reference]	1.04 (0.66- 1.6)	1.06 (0.82- 1.3)	0.668
AGTR1	rs2131127	1.00 [reference]	1.4 (0.87- 2.4)	1.17 (0.85- 1.6)	0.123	1.00 [reference]	1.06 (0.72- 1.5)	1.06 (0.81- 1.3)	0.654
MMP8	rs1892886	1.00 [reference]	0.62 (0.35- 1.2)	0.64 (0.46- 0.89)	0.014	1.00 [reference]	0.82 (0.50- 1.3)	0.89 (0.68- 1.1)	0.304
MPP7	rs1457177	1.00 [reference]	0.54 (0.56- 5.2)	1.2 (0.79- 1.8)	0.540	1.00 [reference]	0.69 (0.11- 4.2)	0.79 (0.56- 1.11)	0.171
TOMM40	rs1160985	1.00 [reference]	0.80 (0.50- 1.2)	1.04 (0.73- 1.4)	0.479	1.00 [reference]	1.1 (0.75- 1.6)	0.92 (0.70- 1.2)	0.748
TOMM40	rs157580	1.00 [reference]	1.9 (1.2- 3.0)	1.5 (1.1- 2.1)	0.002	1.00 [reference]	1.2 (0.85- 1.7)	0.99 (0.75- 1.3)	0.372
CR1	rs6656401	1.00 [reference]	0.50 (0.17- 1.09)	0.60 (0.42- 0.87)	0.001	1.00 [reference]	1.4 (0.67- 3.0)	1.2 (0.91- 1.6)	0.129
CR1	rs3818361	1.00 [reference]	0.54 (0.18- 1.6)	0.43 (0.28- 0.66)	<0.001	1.00 [reference]	1.3 (0.60- 3.2)	1.2 (0.92- 1.7)	0.120
CR1	rs4844609	1.00 [reference]	No observation	0.38 (0.19- 0.79)	0.009	1.00 [reference]	No observation	1.2 (0.71- 2.1)	0.160
CD33	rs3865444	1.00 [reference]	0.74 (0.46- 1.2)	1.03 (0.75- 1.4)	0.414	1.00 [reference]	1.11 (0.74- 1.6)	0.92 (0.71- 1.1)	0.905
PICALM	rs3851179	1.00 [reference]	0.87 (0.51- 1.2)	1.04 (0.75- 1.4)	0.698	1.00 [reference]	1.1 (0.78- 1.6)	0.97 (0.75- 1.2)	0.638
MS4A6A	rs610932	1.00 [reference]	1.04 (0.69- 1.5)	0.85 (0.61- 1.1)	0.990	1.00 [reference]	1.12 (0.79- 1.6)	1.17 (0.89- 1.5)	0.398

MS4A4E	rs670139	1.00 [reference]	1.2 (0.75- 1.9)	0.82 (0.57- 1.1)	0.712	1.00 [reference]	0.70 (0.46- 1.06)	1.01 (0.74- 1.3)	0.167
ABCA7	rs3752246	1.00 [reference]	1.11 (0.54- 2.2)	0.97 (0.70- 1.3)	0.943	1.00 [reference]	0.69 (0.334- 1.4)	1.1 (0.84- 1.4)	0.980
DTNA	rs4458079	1.00 [reference]	2.25 (0.61- 8.3)	0.66 (0.45- 0.95)	0.192	1.00 [reference]	1.4 (0.578- 3.5)	1.18 (0.87- 1.6)	0.193
HTR2C	rs6318	1.00 [reference]	1.2 (0.83- 1.7)	No observation	0.360	1.00 [reference]	0.72 (0.346- 1.4)	0.95 (0.72- 1.2)	0.467
EPHA1	rs11767557	1.00 [reference]	0.56 (0.24- 1.3)	0.92 (0.66- 1.2)	0.242	1.00 [reference]	1.1 (0.655- 2.0)	0.86 (0.66- 1.1)	0.653
SORCS1	rs7093634	1.00 [reference]	0.99 (0.61- 1.6)	1.1 (0.823- 1.5)	0.778	1.00 [reference]	1.13 (0.751- 1.7)	1.12 (0.86- 1.4)	0.416
PPP3R1	rs1868402	1.00 [reference]	1.20 (0.68- 2.1)	1.06 (0.78- 1.4)	0.499	1.00 [reference]	1.3 (0.86- 2.1)	1.1 (0.91- 1.5)	0.103
MAPT/STH	rs3785883	1.00 [reference]	1.01 (0.46- 2.2)	1.1 (0.86-0 .1.6)	0.403	1.00 [reference]	1.3 (0.598- 2.9)	0.89 (0.68- 1.1)	0.760

[1] R is the major allele and C is the minor allele.

[2] Values are 95% Confidence Interval in parentheses (all such values). Adjusted variables in multivariate models included body mass index (kg/m2, continuous), smoking (never, former, current), age, in years (65-74, 75-84, 85+), diabetes (No, Yes), stroke (No, Yes), heart attack (yes or no), cholesterol (mg, continues), and gender (male, female

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CHAPTER 6

SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

Summary

The overall objective of this dissertation was to determine the extent to which dietary factors, erythrocyte membrane fatty acids, and genes are independently associated with C-reactive protein (CRP) concentration among elderly residents of Cache County, Utah. Evidence for the role of inflammation in AD is limited. Epidemiologic and genetic evidence suggest that inflammatory biomarkers are involved in the pathogenesis of AD by releasing inflammatory mediators such as cytokines, chemokines, and neurotransmitters [1]. There is strong evidence of an etiologic role of both genetic and environmental factors with inflammation. Diet and erythrocyte membrane fatty acids (EMFAs), which are considered environmental factors, may influence the risk of AD and through its effects on systemic inflammation [2]. Concomitantly, genes associated with AD may influence AD risk via their effects on inflammation [3].

The results of this dissertation support the roles of nutrition and genes in systemic inflammation as indicated by CRP. Our dietary pattern analysis confirmed the importance of the elderly diet in the etiology of inflammation, which may lower AD risk. Among elderly individuals whose diets highly resembled the ideal high adherence of Dietary Approach to Stop Hypertension (DASH) diet and Mediterranean dietary (MED) patterns, there was a lowered risk of having high CRP levels. Interestingly, a greater reduction in the risk of CRP was found with high accordance of both DASH and MED among overweight and obese compared to normal weight participants.

Eight of the erythrocyte membrane fatty acid concentrations were associated with the inflammatory biomarker CRP. When comparing higher levels of palmitoleic acid and nervonic acids, both monounsaturated fatty acids (MUFAs), dihomo-y-linolenic acid (DGLA), docosapentaenoic acid (DPA-6), docosahexaenoic acid (DHA), all polyunsaturated fatty acids (PUFAs) with lower levels, risk of elevated plasma CRP was lower among the CCMS participants. Conversely, higher levels of margaric acid, stearic acid, and arachidic acid, all saturated fatty acids (SFAs), were associated with a lower risk of elevated CRP. Among those with higher EMFA high levels of pentadecanoic acid, palmitic acid, behenic acid, lignoceric acid, oleic acid, gondoic acid, erucic acid, vaccenic acid, linoleic acid, a-linolenic acid, eicosadienoic acid, arachidonic acid, eicosapentaenoic acid, adrenic acid, docosapentaenoic acid n3, there was no discernable effect on CRP levels.

In our study, we also found an association with APOE-epsilon genotypes and four SNPs of AD-related genes on CRP inflammatory biomarker. APOE-epsilon genotypes were associated with CRP levels among elderly men and women. When data were stratified by gender, major allele of APOE (C/C) rs439401, TOMM40 (A/A) rs157580, and minor allele of MMP8 (T/T) rs1892886, CR1 (A/A) rs6656401, rs3818361, and rs4844609 lowered the risk of elevated CRP among elderly men. Among those with BIN1, CLU, CD2AP, AGTR1, MS4A6A/ MS4A4E, MPP7, ABCA7, CD33, PICALM, DTNA, HTR2C, EPHI1, SORCS1, PPP3R1, and MAPT/STH, there was no significant effect on CRP levels.

Limitations and Future Directions

The dissertation described here provides evidence of the roles that dietary patterns, defined by DASH and MED adherence, erythrocyte membrane fatty acids composition, and AD-related genes, have on the risk of systemic inflammation CRP levels after adjusting for potential confounders. There are some limitations that must be discussed and addressed in future work. Cache County Memory Study does not have a collection of blood for inflammatory biomarkers at the Wave 1 baseline examination that would allow a prospective study of CRP levels and subsequent outcomes. We also used a single inflammatory marker CRP to determine the serum level of inflammatory biomarkers, but it has been proposed that systemic inflammatory markers change over time [4], so examining multiple inflammatory biomarkers would help to strengthen our results.

The following recommendations are also offered for related research on systemic inflammation biomarker CRP:

1. Replication studies are needed to confirm the effect of a DASH diet and MED on systemic inflammation by lowering CRP level among elderly in different populations.

2. Further prospective studies examining erythrocyte membrane fatty acids, including palmitoleic acid, dihomo-y-linolenic acid (DGLA), docosapentaenoic acid (DPA-6), docosahexaenoic acid (DHA), nervonic fatty, margaric acid, stearic acid, pentadecanoic acid, palmitic acid, behenic acid, lignoceric acid, oleic acid, gondoic acid, erucic acid, vaccenic acid, linoleic acid, a-linolenic acid, eicosadienoic acid, arachidonic acid,

eicosapentaenoic acid, adrenic acid, docosapentaenoic acid n3, and arachidic acid, inflammation, and other disease would strengthen the present findings.

3. We examined the association of erythrocyte membrane fatty acid concentration and plasma CRP level in depth, but further examination of the associations between food sources for each fatty acid with EMFA concentration and CRP would be valuable additions regarding these associations.

4. Genotypic imputations, study of additional variants from gene sequencing, and study of gene-nutrient interaction to increase our understanding of systemic inflammation and to further assess the consistency of evidence in terms of both significance and direction of effects observed in our study.

5. Our hypothesis-driven genetic study only assessed individual SNPs and did not take into account correlation among SNPs or genes.

6. Further studies are needed to explore and explain the effects of the interactions between APOE rs157580 and TOMM40 rs439401 on CRP level as a dependent variable, particularly among elderly individuals.

<div align="center">Public Health Significance</div>

Although more research is needed to characterize the relationship between elderly nutrition and the risk of systemic inflammation, healthy elderly diets with adherence to a DASH diet or MED are safe and feasible interventions that may reduce the risk of AD among the elderly by reducing CRP and other inflammatory biomarkers. Fatty acid consumption is still a controversial issue. Thus, more scientists and clinicians need to join in the efforts to understand the impact of FAs on health outcomes.

The discovery of the effects of AD-related genes on CRP may provide clinicians specific targets for more effective intervention strategies. For example, in our study, we observed that the presence of major allele APOE rs439401 and TOMM40 rs157580 and minor allele of MMP8 rs1892886, CR1 rs6656401, rs3818361, and rs4844609 decrease the risk of having elevated CRP levels. Men with the minor allele of APOE rs439401 and TOMM40 rs157580, and major allele of MMP8 rs1892886, CR1 rs6656401, rs3818361, and rs4844609 can be targeted for more aggressive treatment to reduce their CRP levels, which may lower the chance of having AD later in their life.

Reduction in the prevalence of AD could have tremendous importance. The results of this dissertation may help identify factors important to AD etiology and, in turn, provide valuable targets for preventive intervention. Until now, there is no cure for AD; individuals with AD require medical care to maintain quality of life, maximize function in daily activities, foster a safe environment, and enhance cognition, mood, and behavior. The costs incurred in caring for elderly with AD not only include multi-disciplinary clinical care, but also involves emotional disturbance and social and employment exclusion for affected individuals. Reducing the risk of AD would lessen considerable financial and emotional burdens for families and society.

Conclusions

In conclusion, this dissertation presents additional insight into the possible dietary patterns, erythrocyte membrane fatty acids composition, and AD-related genes associated with systemic inflammation. The findings indicate that adherence to dietary pattern DASH and MED influence the risk of systemic inflammation. While saturated erythrocyte membrane fatty acids composition may be anti-inflammatory, MUFAs and

PUFAs may increase the risk of systemic inflammation. Additionally, the results support the hypotheses that AD-related gene alleles affect systemic inflammation.

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CURRICULUM VITAE

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(July 2015)

RESEARCH INTERESTS

Al-zheimer's epidemiology, nutritional epidemiology, clinical epidemiology, and genetic epidemiology and statistical genetics.

EDUCATION

2010-2015	Ph.D.	Utah State University Logan, UT, United States Department of Nutrition and Food Science Emphasis: Nutrition science Dissertation: The role of diet and alzheimer's- related genes in the Cache County Memory Study Major Professor: Ronald Munger, PhD.
2012-2013	B.S.	Utah State University Logan, UT, United States Emphasis: Dietetics
2013-2014	Dietetic Internship	Utah State University CA, United States - Encino Hospital Medical Center (Inpatient, nutrition support, longterm care, nutrition support) - Diabetes Care Pharmacy & Health Education Program (Outpatient Clinical) - The Conejo Valley Unified School District (Child nutrition) - Women, Infants, and Child program (WIC), PHFE (Community nutrition)
2008	M.S.	King Abdulaziz University Jeddah, Saudi Arabia Food and Nutritional Sciences
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PROFESSIONAL EXPERIENCE

03/2008- 05/2008	Aldar Hospital. Madinah, Saudi Arabia Translated the physician written diet order in terms of foods or nutritional products & formulas; assessed, developed, implemented and evaluated nutritional care plans and provided follow up; designed meal patterns individualized according to patients food habits and modified according to therapeutic needs; counseled patients and family of home diet if needed; recommended appropriate formulas for enteral feeding (intravenous); documented patients nutritional care during their hospitalization; participated in evaluation and monitoring of food service system and made recommendation as needed.
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COURSES AND CONFERENCES

1997	Diploma in Computer Application Institute global computer and technical Madinah, Saudi Arabia
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2006	Food & Nutrition issues in Kingdom of Saudi Arabia King Fahd Hospital Jeddah, Saudi Arabia
2006	Symposium assess and control obesity The Arab Center for Nutrition Manama, Bahrain Kingdom
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2007	Medical Information Services Workshop Deanship of Library Affairs- King Abdul-Aziz University Jeddah, Saudi Arabia
2007	Saudi Fourth Conference of food and nutrition King Saud University Riyadh, Saudi Arabia
2011	Alzheimer's Association International Conference Paris, France
2012	Johns Hopkins Bloomberg School of Public Health MB, United States • Introduction to diabetes and obesity epidemiology • Critical reading of epidemiologic literature • Family based genetic epidemiology • Genetic epidemiology in populations