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DIETARY INFLAMMATORY INDEX AND ITS RELATIONSHIP WITH INFLAMMATION, METABOLIC BIOMARKERS AND MORTALITY

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DIETARY INFLAMMATORY INDEX AND ITS RELATIONSHIP WITH
INFLAMMATION, METABOLIC BIOMARKERS AND MORTALITY

by

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DEDICATION

To those who believed.

Thank you to my family, friends, committee, and colleagues who have supported me throughout this academic journey. I could not have done this without you.

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I would like to thank Dr. James R. Hebert, my committee chair and advisor for his continuous support of my efforts to develop the DII and for giving me complete freedom to contact interested researchers around the world. I have certainly been fortunate to have him and very supportive and understanding committee (Dr. Susan Steck, Dr Jim Hussey, and Dr Yunsheng Ma) to guide my research and provide fruitful feedback on my dissertation aims and the entire proposal. I would also like to thank my parents, sister, brother in law and my wife for being with me and for continuously motivating me throughout the entire duration of my journey. I would also like to thank Mr. Tom Hurley and Dr Philip Cavicchia who helped during the process of DII development.

ABSTRACT

Background: Diet and its components are known to play an important factor in the process of inflammation and in turn on the health effects that are related to inflammation like cancer, and cardiovascular diseases. Previous research so far has mainly looked at the effect of specific food or nutrients on inflammation and health outcomes. In this regard a new literature derived and population based dietary index called Dietary Inflammatory Index (DII) was developed after carefully screening around 6000 articles that looked at the association between 45 food parameters and 6 commonly studied inflammatory markers. The list of food parameters includes various nutrients like vitamins, minerals, macronutrients; food items like garlic, onion, ginger; and bioactive compounds flavonoids. The purpose of this research is to explore the following associations: 1. Association between DII and C - reactive protein (CRP) in NHANES 2005-2010; 2. Association between DII and mortality in NHANES III study and 3. Association between DII and inflammatory and metabolic biomarkers in CAN DO intervention study.

Methods: First data from NHANES 2005-2010 was used to examine the association between DII and CRP among the United States population by race/ethnicity and diabetes status. CRP was analyzed as both continuous and as categorical variable (based on the cut-off of 3mg/l). As CRP was not normally distributed it was log transformed and analyzed. In the same dataset HEI-2010 was calculated and used to predict CRP and results were compared with those of DII. Multivariate linear and logistic regression was

used for the analyses. Next, we examined the ability of a newly developed dietary inflammatory index (DII) to predict mortality in the National Health and Nutrition Examination Survey (NHANES) III cohort study. The DII was computed based on baseline dietary intake assessed 24-h dietary recalls (1988-94). Mortality was determined from the National Death Index records through 2006. Cox proportional hazards regression was used to estimate hazard ratios. During the follow-up period through the end of 2006, 2795 deaths were identified, including 615 cancer, 158 digestive cancer and 1233 cardiovascular (CVD) deaths. Following this for the third aim data was used from the CAN DO study, a dietary intervention study with a sample size of 234 individuals with metabolic syndrome. The two interventions were 1) a high fiber diet and 2) the American Heart Association (AHA) diet. DII was calculated using 24-h dietary recalls at baseline, 6, and 12 months and was tested against metabolic markers (insulin, blood glucose and homeostasis model assessment (HOMA-IR)) and inflammatory markers, namely C-reactive protein (CRP), IL-6 and TNF- α using linear mixed models adjusted for covariates. All the biomarkers were log transformed and the results are back-transformed and expressed as the ratio of the geometric means.

Results: Multivariate analysis revealed CRP to be positively associated with DII_{Quartile4vs1} (β =0.19, C.I. 0.13, 0.24), and HEI-2010_{Quartile1vs4} (β =0.15, C.I. 0.10, 0.20). Similar associations were observed when CRP was categorized (>3 mg/l), DII_{Quartile4vs1} (OR= 1.37, C.I. 1.27, 1.71), and with HEI-2010_{Quartile1vs4} (OR= 1.31, C.I. 1.12, 1.56).

Multivariable analysis, adjusting for , race, diabetes status, hypertension, physical activity, BMI, poverty index and smoking, revealed positive associations between higher DII and overall mortality (HR for DII Tertile3vs1=1.34; 95%CI 1.19- 1.51, p-trend-

<0.0001), cancer related mortality (HR for DII Tertile3vs1=1.46; 95%CI 1.10- 1.96, p-trend-0.01), digestive cancer mortality (HR for DII Tertile3vs1=2.10; 95%CI 1.15- 3.84, p-trend-0.03) and CVD mortality (HR for DII Tertile3vs1=1.46; 95%CI 1.18- 1.81, p-trend-0.0006). Across time points DII was lower in the ‘high fiber’ group compared to the ‘AHA’ group. For metabolic factors after multivariate analysis compared to tertile 1 participants in tertile 3 had higher insulin level (1.41; 95% CI 1.02, 1.91), glucose level (1.07; 95% CI 1.02, 1.12) and HOMA-IR (1.51; 95% CI 1.07, 2.09) and for inflammatory biomarkers, compared to tertile 1 participants in tertile 3 had higher IL-6 values (1.35; 95% CI 1.05, 1.78). No significant associations were observed with CRP and TNF- α .

Conclusion: The results from all the three aims reinforce the fact that diet as a whole plays an important role in modifying inflammation and health outcomes related to inflammation. Results from aim 1 show the DII can predict inflammation in general population with different ethnicities and from different regions of US and also comparatively DII has a slightly better predictive ability (6%) compared to HEI-2010. Results from second aim showed that a pro-inflammatory diet, as indicated by higher DII scores, was associated with overall, cancer and CVD mortality and finally results from the intervention study provide further evidence that fiber has a major effect in reducing inflammation and insulin resistance and also reinforce the opinion that DII can be used as a tool to detect the levels of metabolic and inflammatory biomarkers. Finally all the above mentioned results suggest that diet has a major role in controlling inflammation and thereby plays an important role in the development or prevention of various chronic diseases, hence public health steps should be taken to modify individual’s whole diet rather than the intake of specific nutrients.

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LIST OF ABBREVIATIONS

24HR	24 hour dietary recall
AHA	American Heart Association
AHEI	Alternate Healthy Eating Index
BMI	Body Mass Index
CDC	U.S. Centers for Disease Control and Prevention
CHD	Coronary heart disease
CRC.....	Colorectal cancer
CRP	C-reactive protein
CVD	Cardiovascular disease
DII	Dietary Inflammatory Index
DM	Diabetes Mellitus
HEI.....	Healthy Eating Index
HDL	High-density lipoprotein
HOMA-IR.....	Homeostasis model assessment
IL.....	Interleukin
MetSyn.....	Metabolic Syndrome
NHANES	National Health and Nutrition Examination Survey
TNF- α	Tumor Necrosis Factor-alpha

CHAPTER 1

Introduction

Statement of the Problem

Acute inflammation is the body's natural response to tissue injury, which helps heal wounds and promote tissue regeneration (Thun, Henley et al. 2004; Keibel, Singh et al. 2009; Pan, Lai et al. 2009; Warnberg, Gomez-Martinez et al. 2009). When this process of inflammation is not controlled properly, a chronic low-grade inflammatory state could result (Warnberg, Gomez-Martinez et al. 2009). Chronic inflammation has been shown to be associated with many chronic conditions and outcomes, such as cancer incidence, cancer-related deaths, cardiovascular disease, respiratory disease, obesity, and insulin resistance (Mohamed-Ali, Goodrick et al. 1997; Bastard, Jardel et al. 2000; Pearson, Mensah et al. 2003; Thun, Henley et al. 2004; Kristan 2013; Lee and Yang 2013).

Dietary factors also have been associated with inflammation. The Western-type diet, which is high in red meat, high-fat dairy products, and refined grains, has been associated with higher levels of CRP, IL-6 and fibrinogen (King, Egan et al. 2003; Johansson-Persson, Ulmius et al. 2013). On the other hand, the Mediterranean diet, which is high in whole-grains, fruit and green vegetables, fish, low in red meat and butter, with moderate alcohol and olive oil intake, has been associated with lower levels of inflammation (Estruch, Martinez-Gonzalez et al. 2006). Vegetarian diets such as the

Macrobiotic diet has been known to reduce body fat and body mass index (BMI) and biochemical indicators such as serum glucose and lipids.(Porrata-Maury, Hernandez-Triana et al. 2012) Diets high in fruits and vegetables have been associated with lower levels of CRP (Esmailzadeh, Kimiagar et al. 2006). Specific nutrients also have consistently been shown to be associated with lower levels of inflammation, such as carbohydrates (Kitabchi, McDaniel et al. 2013), omega-3 PUFA (Ferrucci, Cherubini et al. 2006), fiber (Ma, Griffith et al. 2006), moderate alcohol intake (Avellone, Di Garbo et al. 2006), vitamin E (Bertran, Camps et al. 2005), vitamin C (Wannamethee, Lowe et al. 2006), β -carotene (Erlinger, Guallar et al. 2001), and magnesium (King, Mainous et al. 2005).

Studies have shown chronic inflammation to be associated with cancers of the colon, breast, prostate, lung, and other sites (Thun, Henley et al. 2004; Moossavi, Zhang et al. 2013; Toriola, Laukkanen et al. 2013) and cancer specific mortality(Sedlacek, Playdon et al. 2011; Cooney, Chai et al. 2013). Results from epidemiologic studies indicate a positive association between inflammatory markers and colorectal cancer (Maihofner, Charalambous et al. 2003; Erlinger, Platz et al. 2004; Nikiteas, Tzanakis et al. 2005), breast cancer (Ollberding, Kim et al. 2013) and prostate cancer (Kim, Jeon et al. 2013).

In 2009, approximately 136,717 people were diagnosed with colorectal cancer (CRC) and 51,848 people died of the disease.(2013) In the United States, CRC is the second leading cause of cancer-related deaths and third most commonly diagnosed cancer among men and women (2013). Breast cancer is the leading cancer among women in United States and, largely owing to its high incidence, is one of the leading causes of

cancer-related deaths among women;(2013) in 2009, 211,731 breast cancer cases were diagnosed and 40,676 women died of breast cancer.(2013) Analogously, in males, prostate cancer is the most commonly diagnosed cancer and is one of the leading causes of cancer-related deaths; 206,640 men were diagnosed with prostate cancer in 2009 and 28,088 prostate cancer-related deaths were reported.(2013)

Metabolic syndrome (MetSyn) consists of a cluster of several metabolic and physiological abnormalities, including obesity, impaired glucose regulation, dyslipidemia and hypertension. As per the analysis conducted on adults population from NHANES 2003-2006, 34% of adults met the criteria for MetSyn which indicates that this disease is widely prevalent in the general population(Ervin 2009). It has become a subject of paramount interest in both research and clinical medicine, owing to its association with the increased risk of developing type 2 diabetes and atherosclerotic cardiovascular disease (CVD)(Ford 2005). While several theories have been proposed in the etiology and progression of metabolic syndrome (MetSyn), they all tend to point to inflammation as a key factor in the pathogenesis of the disease(Grundy 2003). Therefore, treating or preventing the progression of this disease through modifications of modifiable life-style factors, such as dietary behaviors is crucial.

Several aspects of diet have been associated with all cause mortality and cause specific mortality (cancer and CVDs mortality). Chronic inflammation is known to be associated with common epithelial cancers, with colorectal (Chung and Chang 2003; Terzic, Grivennikov et al. 2010; Toriola, Cheng et al. 2013) being the most intensively studied. Worldwide, CVD is the leading cause of mortality, accounting for about half of the deaths among adults (2008). In the United States, more than 80 million people suffer

from CVD, and an average of about one million Americans die each year (Calabro, Golia et al. 2009; Lloyd-Jones, Adams et al. 2009). There is growing evidence that specific dietary components influence inflammation (de Mello, Schwab et al. 2011; Khoo, Piantadosi et al. 2011; Luciano, Mottus et al. 2012) and all-cause, cancer and cardiovascular disease (CVDs) mortality.(Cohen, Hailpern et al. 2008; Deng, Song et al. 2013; Chang, Lazo et al. 2014; Cheung, Sahni et al. 2014) Previous studies also have examined the effect of specific food items, such as red meat,(Pan, Sun et al. 2012; McCullough, Gapstur et al. 2013; Takata, Shu et al. 2013; Larsson and Orsini 2014) and nutrients, such as calcium,(Li, Kaaks et al. 2011) magnesium(Li, Kaaks et al. 2011) and vitamin E,(Pocobelli, Peters et al. 2009) and their association with mortality. No association was observed between magnesium and calcium and cancer related mortality in EPIC-Heidelberg study (Li, Kaaks et al. 2011) and in a prospective study conducted by Pocobelli et al., vitamin E was found to significantly reduce CVD mortality but no association was observed with cancer mortality (Pocobelli, Peters et al. 2009).

Diet also has been shown to be associated with all-cause mortality, a low carbohydrate diet from animal source has been shown to have an positive association with all cause mortality than a low carbohydrate diet from plant sources (Fung, van Dam et al. 2010), and fruit and vegetables consumption has been shown to have an inverse association with all cause mortality(Bellavia, Larsson et al. 2013). A number of studies have assessed the relationship between MetSyn and diets; inverse association has been observed between diets high in fruits and vegetables and MetSyn (Esmailzadeh, Kimiagar et al. 2006; Fonseca, Gaio et al. 2012). Mediterranean style diet has been

shown to reduce the levels of inflammatory markers among patients with MetSyn(Esposito, Marfella et al. 2004).

The Healthy Eating Index (HEI) was first developed in 1995 to indicate the extent to which an individual's diet adheres to official guidelines described in the United States Department of Agriculture Food Guide Pyramid and was later updated to create versions in 2005 (HEI-2005) and 2010 (HEI-2010) (Kennedy, Ohls et al. 1995; Guenther, Reedy et al. 2008; Guenther, Casavale et al. 2013). The 12 components of HEI-2010 are total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories (Guenther, Casavale et al. 2013). HEI has been used previously to predict inflammation and health-related outcomes (Boynton, Neuhouser et al. 2007; Shahril, Sulaiman et al. 2013).

Over the past five years we have developed a Dietary Inflammatory Index (DII) that can be used in different datasets across diverse population in order to predict levels of inflammatory markers and related health outcomes.(Shivappa, Steck et al. 2013) The goal in creating the DII was to provide a tool that could categorize individuals' diets on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. We have recently substantially modified the DII since the original publication in 2009.(Cavicchia, Steck et al. 2009) The new version which has recently been accepted for publication works the same way (i.e., we multiply the food parameter-specific scores by the actual amounts eaten – as reported on ANY dietary assessment). The differences in the new DII are: 1) that the literature base is more robust owing to extended literature review from 2008-2010 (1943 articles vs. <1000) 2) The list of food parameter were increased to 45

which included both food items and nutrients and 3) we standardize to the world average intake to avoid the arbitrariness that would arise by using raw amounts (ug, mg, kcal and gms) for each food parameter. We were successful in fitting this DII to two different sources of dietary intake information [24 hour recall (24HR) and 7DDR] in order to predict hs-CRP in a longitudinal study of diet and inflammation. We have been able to validate it successfully with inflammatory markers in National Health and Nutrition Examination Survey (NHANES), Seasonal Variation of Blood Cholesterol Levels Study and UK Dietary and Nutrition Survey. However, we have not evaluated the effect of changes in the DII in a dietary intervention trial and associated them with changes in metabolic health and inflammatory markers among participants with MetSyn.

Purpose & Objectives

The DII was validated using the SEASONS data which included nutrient and food information, and majority of the participants in this study were European Americans.(Merriam, Ockene et al. 1999) By contrast, NHANES is a complex, stratified, multistage probability sample designed to provide prevalence estimates describing the health and nutritional status of the civilian, non-institutionalized US population and which included people from different racial/ethnic backgrounds. Dietary data from NHANES are derived from two 24HR interviews and are limited to nutrient information. Therefore our first objective will be a sensitivity analysis to determine the association between DII calculated using only nutrient information and hs-CRP as outcome in NHANES 2005-2010. We will then calculate HEI-2010 scores in NHANES 2007-2008 dataset and conduct a similar analysis with hs-CRP as outcome and compare the results from the two analyses.

The second objective of this dissertation is to determine the relationship between DII and overall mortality, cancer related mortality and CVD mortality. Specifically, we will evaluate the association between DII and 1) all cause mortality, 2) cancer mortality, 3) digestive cancer-related mortality and 4) CVDs mortality. The above-mentioned mortality data are available in the NHANES follow-up study, wherein mortality is ascertained based upon probabilistic matching between NHANES III and National Death Index death certificate records. The mortality linkage methodology is described in detail elsewhere.(2009)

The third objective of this dissertation is to use DII in an intervention trial. We intend to first calculate DII for all the eligible participants with MetSyn in the 2 intervention groups of the CAN DO study(Merriam, Ma et al. 2009) who are randomized in to either of the following two dietary interventions: American Heart Association (AHA) recommended diet and High Fiber (HF) diet. DII will be calculated based on the foods and nutrient intake which is determined by multiple 24 HR recalls at each time point and subsequently fit a mixed model to evaluate the relationships between changes in DII and changes in blood pressure, lipid profiles, fasting glucose, insulin, HOMA-IR, HBA1_C, hs-CRP, TNF- α , and IL-6; we will also compare the two intervention groups by looking at the mean change in DII across time in the two groups.

In all the above analyses DII will be used both as a continuous variable and as a categorical variable. Logistic and linear regression will be carried out for objective one. Survival analysis will be carried out to obtain Hazard Ratios (HR) for the effect of DII score on overall and cancer specific mortality (objective two) and for objective three, mixed analysis will be carried out.

AIM 1: Determine the relationship between DII and hs-CRP in NHANES 2005-2010 data and compare the results with those obtained from HEI-2010 and hs-CRP.

Hypothesis: A pro-inflammatory diet (higher DII score) is associated with an increased odds of elevated hs-CRP ($>3\text{mg/L}$). Also, we hypothesize that odds ratio and chi-square values will be better for results with DII than with HEI-2010.

AIM 2: Determine the relationship between DII and all cause mortality, cancer mortality, digestive cancer mortality and CVDs mortality.

Hypothesis: People with a pro-inflammatory diet (higher DII scores) are at higher risk of dying in general and are also at higher risk of dying from cancer, digestive tract related cancer deaths and CVDs related death.

AIM 3: Determine the relationship between DII and blood pressure, lipid profiles, fasting glucose, insulin, HOMA-IR, HBA1_C, hs-CRP, TNF- α , and IL-6 in people with MetSyn in the two intervention arms of the CAN DO study.

Hypothesis: The mean change in DII between baseline visit and 12 months visit, in the high fiber diet is more than the mean change in DII in the American Heart Association diet.

Significance of Research

One of the main goals of this research is to determine if the DII is associated with inflammation as evidenced by elevated levels of CRP, overall and cancer specific mortality and to examine the effect of dietary interventions on the change in DII. Significant findings would provide additional evidence for the validity of the DII and its

ability to provide a way to develop measures to prevent or slow the development of cancers and improve quality of life among people with cancers.

Aim 1 of this dissertation will determine the sensitivity of the DII to predict hs-CRP in NHANES which has only nutrient data and is representative of the general population of U.S. Significant findings in this analysis will demonstrate the robustness of DII and its ability to summarize the inflammatory potential of the diet using fewer food parameters across a wider range of population from different races and regions as a result of which researchers can use DII in any epidemiologic study. Improved findings with DII compared to HEI-2010 will encourage researchers to use a dietary index which is scientifically sound and is a product of the very careful and meticulous process involved in reviewing and scoring the scientific literature over many years of research on diet and inflammation, and obtaining data sets from around the world to which we could relate individuals' dietary intakes which is entirely absent from virtually all of currently available dietary indices. Because of the relative ease of use, the DII also should be appropriate for clinical applications.

Aim 2 of this dissertation seeks to determine the association between the DII and mortality. Significant findings from aims 2, because of the prospective study design, will provide evidence for temporality and the protective effect of the DII. Aspects of diet and chronic inflammation have both been shown to be associated with overall mortality and cause-specific mortality. Evidence of a protective effect of the DII on these outcomes can provide additional evidence of the association and the possible causal pathways between diet and various inflammation related specific mortalities.

Aim 3 of this dissertation seeks to determine the effect of DII in an intervention trial with multiple outcomes in two treatment groups, one with a high-fiber diet intervention and another with AHA recommended intervention. Outcomes used for this analyses include measures of cardiovascular diseases (blood pressure, lipid profiles), impaired glucose metabolism (fasting glucose, insulin, HOMA-IR, HBA1_C), and inflammatory markers (hs-CRP, TNF- α , and IL-6). Hence, significant results based on these outcomes will provide evidence for future usage of DII in epidemiological studies which has these outcomes. Also, finding improvements in the DII score in high fiber diet group compared to AHA recommended diet group proves the hypothesis from the researchers of CAN DO study that high fiber condition significantly improves the overall diet quality and metabolic health over the AHA condition (Merriam, Ma et al. 2009).

Study Outline

Chapter 2 of this dissertation provides detail about chronic inflammation and the effects of diet on inflammation. The DII is then described in detail, including the concept/idea, development of the method, and its validation. Then, each outcome of interest is described separately and their associations with diet and inflammation. Chapter 3 discusses the methods used for each aim, including background information on the data sources, type of data collected, and analytical methods. Chapter 4 will be the manuscript for aim 1, 'Validation of the DII in NHANES 2005-2010 with hs-CRP as outcome and comparison with the HEI-2010 for NHANES 2005-2010 dataset.' Chapter 5 will be the manuscript for aim 2, 'Association between DII and mortality in NHANES III.' Chapter 6 will be the manuscript for aim 3, 'Association between DII and metabolic and inflammatory biomarkers in CAN DO intervention study'. Chapter 7 is then an

overall summary of the findings from this dissertation. This chapter will include a summary of each of the findings and an overall synthesis of the results, suggestions for future research, and conclusions.

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CHAPTER 2

Background & Significance

Chronic Inflammation

Inflammation is a result of body's response to tissue insult/injury or the presence of inflammatory stimulants (Keibel, Singh et al. 2009; Pan, Lai et al. 2009) and is an important step in the process of wound healing and tissue regeneration, which under normal circumstances will lead to recovery within a few days. (Thun, Henley et al. 2004; Warnberg, Gomez-Martinez et al. 2009) The above mentioned scenario described acute inflammatory response and it can lead to chronic low-grade inflammatory state if not controlled appropriately.(Warnberg, Gomez-Martinez et al. 2009) Chronic inflammation is defined as a persistent condition where tissue destruction and repair occur at the same time (Coussens and Werb 2002; Philip, Rowley et al. 2004) and this occurs as a result of continuous recruitment of pro-inflammatory cytokines and the inability to resolve the damage due to decreased production and decreased mobilization of anti-inflammatory cytokines. (Coussens and Werb 2002) Increased blood flow to the injured tissue, due to histamine released by damaged mast cells, results in efficient recruitment of inflammatory cells, such as cytokines, neutrophils, and monocytes (Keibel, Singh et al. 2009). Pro-inflammatory cytokines, such as c- reactive protein (CRP), interleukin-1 β

(IL- β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) are expressed to remove foreign pathogens and to attract immune cells to the damaged site. (Pan, Lai et al. 2009) As mentioned previously if this acute phase reaction is uncontrolled then it can lead to a chronic state of inflammation and in order to keep this in check body releases endogenous antagonists in the form anti inflammatory cytokines like interleukon-4 (IL-4) and interleukin-10 (IL-10). (Torre, Tambini et al. 2000; Simhan, Chura et al. 2004)

Acute-phase proteins, such as hs-CRP), IL-6 and TNF- α are good markers of inflammation with hs-CRP being the most studied marker. (Sarwar, Thompson et al. 2009) Very high levels of Hs-CRP in blood (>10mg/l) are seen in response to acute inflammation. (Hamer and Chida 2009) (Danesh, Whincup et al. 2000; Griffith, Ma et al. 2008) On the other hand, slightly elevated levels of hs-CRP are a result of a possible chronic inflammatory state. (Griffith, Ma et al. 2008; Hamer and Chida 2009) Another property of hs-CRP that is responsible for its wide use in research is its long stable half life (19 hours) as a result of which it can be measured at any time of the day. (Calabro, Golia et al. 2009)

Another well studied marker of inflammation is IL-6. IL-6 is a pro-inflammatory cytokine produced by mononuclear cells (monocytes, macrophages, and lymphocytes), endothelial cells, mast cells, astrocytes, and microglia. (Papanicolaou, Wilder et al. 1998) Transcription factors, such as NF κ B have been shown to activate the expression of IL-6. (Matsusaka, Fujikawa et al. 1993) Also, IL-6 has the ability to activate NF- κ B pathways. (Yoshimura 2006) IL-6 stimulates the production of acute-phase proteins, such as CRP (Erlinger, Platz et al. 2004). IL-6 has not been studied as much as CRP, probably

because of greater within-person variability and short half-life (<2h compared to 19h for CRP).(Danesh, Kaptoge et al. 2008)

Another pro-inflammatory cytokine which is well studied is tumor necrosis factor (TNF- α) which is produced by activated macrophages and other cells in response to tissue injury or chronic inflammation.(Mirza, Hossain et al. 2012) Through its pro-inflammatory actions, TNF- α may play a role in cancer growth and metastasis by inducing reactive oxygen species.(Balkwill 2009; Mirza, Hossain et al. 2012) Like IL-6, one of the main reasons for its limited use in research is its extremely short half life.(Beutler, Milsark et al. 1985)

Effects of Diet on Inflammation

Diet and dietary factors have been shown to have an effect on inflammation.(de Mello, Schwab et al. 2011; Khoo, Piantadosi et al. 2011; Krishnamurthy, Wei et al. 2012; Luciano, Mottus et al. 2012) Researchers have used different approaches to investigate this link between diet and inflammation which include investigating the relationship between inflammation and dietary patterns or whole foods or specific nutrients or food constituents. While investigating dietary patterns, an individual's whole diet is taken into consideration. There are different types of dietary patterns like for example Mediterranean diet which is high in whole-grains, fruit and green vegetables, fish, low in red meat and butter, with moderate alcohol and olive oil intake, has been associated with lower levels of inflammation.(Estruch, Martinez-Gonzalez et al. 2006) Vegetarian diet like macrobiotic diet has been known to reduce anthropometric variables like body fat, BMI and biochemical indicators like serum glucose and lipids(Porrata-Maury, Hernandez-Triana et al. 2012) and on the other hand diet rich in red meat, high-fat dairy

products, and refined grains (Western diet), has been associated with higher levels of CRP, IL-6 and fibrinogen . In some research publications, diets are scored in the form of various indices like Healthy Eating Index (HEI), and Mediterranean Diet scores (MedS) and the associations between indices and inflammation have been investigated (Serrano-Martinez, Palacios et al. 2005; Boynton, Neuhouser et al. 2007) Some studies have focused on the inflammatory effects of whole foods. For example, diets high in fruits and vegetables have been associated with lower levels of CRP (Esmailzadeh, Kimiagar et al. 2006) and on the other hand diets high in red and processed meat have shown to be associated with higher CRP and cancer.(Pan, Lai et al. 2009; Viscogliosi, Cipriani et al. 2013) The major problem with this is that when consumed these whole foods are usually eaten with other foods items like salt, sugar, and syrup which may attenuate or accentuate the actual effects of whole food under study but on the other hand the advantage of this using whole foods is that it takes in to account the effects of various nutrients. Other studies have looked at the effects of specific nutrients in relation to inflammation and disease. Specific nutrients have also consistently been shown to be associated with lower levels of inflammation, such as carbohydrates,(Kitabchi, McDaniel et al. 2013) omega-3 PUFA, (Ferrucci, Cherubini et al. 2006) fiber, (Ma, Griffith et al. 2006) moderate alcohol intake, (Avellone, Di Garbo et al. 2006) vitamin E, (Bertran, Camps et al. 2005) vitamin C, (Wannamethee, Lowe et al. 2006) β -carotene, (Erlinger, Guallar et al. 2001) and magnesium. (King, Mainous et al. 2005) Issue with this kind of research are that nutrient is never consumed alone in a diet and hence a nutrient effect may not be independent of the effect of other nutrients in the diet and another issue is the high correlation between nutrients among foods, with a resulting in a loss of statistical

power due to multicollinearity issues.(Fraser 2003) The following paragraphs will discuss the association between dietary patterns, whole foods, and specific nutrients and constituents in relation to inflammation.

Dietary Patterns

Different dietary patterns have different effects on inflammation and chronic diseases. Mediterranean diet is shown to have a protective against inflammation and a number of chronic conditions, such as diabetes, CVD, and cancer. (Chrysohoou, Panagiotakos et al. 2004; Esposito, Marfella et al. 2004; Serrano-Martinez, Palacios et al. 2005; Dalziel, Segal et al. 2006; Estruch, Martinez-Gonzalez et al. 2006; Michalsen, Lehmann et al. 2006; Mitrou, Kipnis et al. 2007; Dai, Miller et al. 2008; Djuric, Ren et al. 2009; Panagiotakos, Dimakopoulou et al. 2009; Rallidis, Lekakis et al. 2009; Luciano, Mottus et al. 2012; Viscogliosi, Cipriani et al. 2013) A recent cohort study in the elderly showed significant inverse associations between a Mediterranean diet and hs-CRP. (Luciano, Mottus et al. 2012) The results have been consistent across most of the observational studies that have studied the association between Mediterranean dietary lifestyle and inflammation. Mediterranean diet has also been used in many dietary intervention trials. Some studies did not find an association,(Rodríguez-Villar, Pérez-Heras et al. 2004; Lapointe, Goulet et al. 2005) but other randomized trials that have implemented a Mediterranean-type diet showed significant decreases in levels of inflammation among individuals in the intervention group.(Estruch 2010) (Esposito, Marfella et al. 2004; Estruch, Martinez-Gonzalez et al. 2006; Michalsen, Lehmann et al. 2006; Djuric, Ren et al. 2009; Rallidis, Lekakis et al. 2009) Jonsson *et al.* conducted a study in which showed the beneficial effects of Paleolithic diet on cardiovascular risk

factor.(Jonsson, Granfeldt et al. 2009) Western dietary pattern (High in refined grains, red and processed meats, high-fat dairy products, and low in fruits and vegetables) has been shown to increase hepatic inflammation (Rivera, Gaskin et al. 2010) and produce inflammatory milk among mothers who consume western food during lactation,(Du, Yang et al. 2012) in another study comparing the effects of western diet on inflammation with those from prudent diet (high in fruits, vegetables and whole grains), significant positive associations were seen between western diet and hs-CRP and IL-6.(Lopez-Garcia, Schulze et al. 2004) Compared to omnivorous diet, vegetarian diet was shown to have an inverse association with hs-CRP in another dietary intervention trial.(Chen, Lin et al. 2008)

Studies looking at diet as a whole have consistently shown that healthy diet have an anti-inflammatory effect among individuals who consume it.

Dietary Indices

Over the past several years, a wide variety of dietary indices have been developed to score an individual's diet which would indicate if they are consuming healthy food or unhealthy food. One such index is Healthy Eating Index (HEI). HEI was first developed in 1995 to indicate the extent to which an individual's diet adheres to official guidelines described in the United States Department of Agriculture Food Guide Pyramid and was later updated to create versions in 2005 (HEI-2005) and 2010 (HEI-2010). (Kennedy, Ohls et al. 1995; Guenther, Reedy et al. 2008; Guenther, Casavale et al. 2013) The 12 components of HEI-2010 are total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories. (Guenther, Casavale et al. 2013) HEI has been used

previously to predict inflammation and health related outcomes. (Boynton, Neuhouser et al. 2007; Shahril, Sulaiman et al. 2013) Another index which is used by researchers is Alternate Healthy Eating Index (AHEI) which was developed as an improvement on original HEI in 2002, to incorporate macronutrients sources which are known to reduce chronic diseases .(McCullough, Feskanich et al. 2002) AHEI 2002 is comprised of 9 components, 8 of which (eg, vegetables, *trans* fat) are scored from 0–10 points to the total score; with a score of 10 indicating complete adherence to the dietary recommendations and on the other hand a score of 0 represents no adherence to the dietary recommendation which indicates a least healthy dietary behavior. The 9th component is multivitamin intake which is scored as either 2.5 points (for nonuse) or 7.5 points (for use). All individual component scores were then summed up to get an overall AHEI score which ranged from 2.5 (worst) to 87.5 (best). (McCullough, Feskanich et al. 2002) This index was updated in 2010 to include additional dietary factors that were known to be associated with chronic diseases and the upper range of the score was now increased to 110 (Chiuve, Fung et al. 2012) and this index has been validated with chronic diseases.(Chiuve, Fung et al. 2012) A Mediterranean diet score (MedS) was created to indicate the adherence of an individual's diet to Mediterranean dietary pattern, which was based on intake of 11 food groups and each food group was scored from 0 (indicating no consumption) to 5 (indicating consumption of more than 18 servings per month), individual food scores are then added up to get the overall MedS which could range from 0 to 55.(Panagiotakos, Pitsavos et al. 2006) Association between MedS and chronic diseases like CVDs has been explored in the past.(Panagiotakos, Pitsavos et al. 2006; Panagiotakos, Pitsavos et al. 2007)

Whole Foods

As mentioned previously, looking at the effect of whole foods on inflammation and chronic diseases has its share of advantages and disadvantages. Some of the food that are known to have anti-inflammatory effects are fruits, vegetables, whole grains, soy products, sea weed, salmon, green tea, ginger and garlic and foods that are known to have a pro-inflammatory effect are red and processed meat, refined grains, sugars and common cooking oils.

Fruits and vegetable are generally considered to be good for health and are known to protect people from inflammation and chronic diseases. In an intervention trial conducted by Peluso et al., ingestion of fruit juice significantly inhibited the high fat diet induced increase in inflammatory markers.(Peluso, Raguzzini et al. 2012; Peluso, Villano et al. 2013) A number of studies have shown an inverse association between fruits and vegetable intake and hs-CRP levels, (Gao, Bermudez et al. 2004; Watzl, Kulling et al. 2005; Esmailzadeh, Kimiagar et al. 2006; Wood, Garg et al. 2012) IL-6,(Root, McGinn et al. 2012) TNF- α (Root, McGinn et al. 2012) and plasma homocysteine levels. (Mietus-Snyder, Shigenaga et al. 2012) (Samman, Sivarajah et al. 2003; Kawashima, Madarame et al. 2007) Orange juice consumption has been shown to significantly decrease levels of hs-CRP, IL-6, and TNF- α .(Devaraj, Jialal et al. 2011; Buscemi, Rosafio et al. 2012) Also, a study done by Huebbe *et al.* found that higher intakes of black currant juice reduced the levels of pro-inflammatory cytokines. (Huebbe, Giller et al. 2012) However one study showed an inverse effect of fruits in hs-CRP but no effect of vegetables.

(Hickling, Hung et al. 2008) Findings show a possible anti-inflammatory effect of fruits and vegetables.

Findings on the relationship between whole grain and inflammation has been mixed so far, the anti-inflammatory effects of whole has largely been attributed to fiber content. Some studies have shown an inverse association between whole grain and inflammation, (Jensen, Koh-Banerjee et al. 2006; Gaskins, Mumford et al. 2010) some studies have shown no effect of whole grain on inflammation.(Andersson, Tengblad et al. 2007; Brownlee, Moore et al. 2010) A study conducted by Masters et al., showed a significant inverse association between whole grain and hs-CRP but no effect was seen other inflammatory markers like fibrinogen. (Masters, Liese et al. 2010) An intervention study comparing individuals randomized to a whole grain diet compared to a refined grain diet found that those in the whole grain group had significantly lower hs-CRP after the intervention compared to the refined grain group.(Katcher, Legro et al. 2008) Further research is needed to prove the true inflammatory nature of whole grains, there could be other factors in whole grains which could mask the anti-inflammatory effect of fiber.

Soy and its products are rich in many anti-inflammatory nutrients likes, polyunsaturated fat, fiber, calcium, and vitamins, are the richest sources of a group of phytoestrogen called isoflavones and are low in saturated fat.(Messina 1999) In a cross sectional study carried by Wu et al., significant inverse associations were observed between quintiles of soy food intake and serum IL-6 and TNF-a levels.(Wu, Shu et al. 2012) Intake of soy products has also been shown to have a protective effect against coronary heart diseases.(Zhang, Shu et al. 2003; Kokubo, Iso et al. 2007) However, results from two clinical trials have shown no beneficial effect of soy products in

reducing the levels of inflammatory markers. (Beavers, Serra et al. 2010) (Miraghajani, Esmailzadeh et al. 2012) So, as observed with whole grain, soy products have also shown mixed results.

Most fishes have high levels of omega 3 fatty acids, with salmon fish being one of the richest sources. A couple of intervention trials have observed significant inverse associations between salmon fish consumption and inflammation.(Pot, Geelen et al. 2010; Ramel, Martinez et al. 2010) In the Ramel et al., study the group which consumed salmon had a greater effect in reducing inflammatory markers (CRP and IL-6) than the remaining three groups that consumed cod, fish oil capsules and sunflower oil respectively (Ramel, Martinez et al. 2010) and in the trial conducted by Pot et al., significant inverse associations were observed between salmon fish consumption and cod fish consumption group, and serum hs-CRP levels.(Pot, Geelen et al. 2010) The anti-inflammatory effect of salmon fish consumption is mainly attributed to high omega 3 fatty acids content.

Among spices turmeric, ginger and garlic have very high anti-inflammatory effects. Turmeric is a spice that is extensively used as a culinary agent in many of Indian dishes. Curcumin is an important phytochemical constituent of turmeric which is responsible for the anti-inflammatory effect of turmeric. (Kapakos, Youreva et al. 2012) Although there are not many human studies conducted to investigate the anti-inflammatory effects of turmeric, evidence from cellular and animal studies show the protective effect of turmeric against inflammation , proliferation of cancer cells and inflammatory bowel diseases. (Baliga, Joseph et al. 2012) (Kim, Noh et al. 2012; Shytle, Tan et al. 2012) Turmeric has been shown to decrease pr-inflammatory markers, such as,

CRP, (Ilsley, Miller et al. 2005) IL-1 β , (Kim, Kim et al. 2005; Okunieff, Xu et al. 2006; Cho, Lee et al. 2007; Kowluru and Kanwar 2007; Reyes-Gordillo, Segovia et al. 2007) IL-6, (Chan, Fong et al. 2003; Wessler, Muenzner et al. 2005; Gulcubuk, Altunatmaz et al. 2006; Kaur, Tirkey et al. 2006; Nonn, Duong et al. 2007) and TNF- α ; (Baliga, Joseph et al. 2012) (Baek, Kang et al. 2003; Gao, Kuo et al. 2004; Bhattacharyya, Mandal et al. 2007; Bruck, Ashkenazi et al. 2007; Woo, Kang et al. 2007) and increase anti-inflammatory cytokines like IL-4. (Shytle, Tan et al. 2012) (Kang, Song et al. 1999; Zhang, Deng et al. 2006) In a pilot intervention study conducted by Holt et al., curcumin reduced the levels of CRP in 4 of the 5 patients with IBD who were administered curcumin, (Holt, Katz et al. 2005) in another pilot intervention study conducted in patients with pancreatitis curcumin significantly reduced erythrocyte malonyldialdehyde and glutathione compared to the placebo. (Durgaprasad, Pai et al. 2005) The anti-inflammatory effects of curcumin are mainly seen in animal and cell studies so far and more human studies are needed to demonstrate its effects in humans. [6]-gingerol, [8]-gingerol, and [6]-shogaol are the active compounds found in ginger that are responsible for its anti-inflammatory effects. (Townsend, Siviski et al. 2013) Like with turmeric most of the studies looking at the relationship between inflammation and ginger have been conducted in animal and cell lines. (Frondoza, Sohrabi et al. 2004; Grzanna, Phan et al. 2004; Lantz, Chen et al. 2007; Nonn, Duong et al. 2007; Levy and Simon 2009) Most studies have shown ginger to reduce inflammation and in one study conducted in mice, ginger inhibited lung and colon carcinogenesis in mice. (Kim, Miyamoto et al. 2009) One human intervention trial showed significant symptomatic relief among patients with rheumatism and musculoskeletal disorders after consumption of powdered ginger extract.

(Srivastava and Mustafa 1992) 1, 2-vinyldithiin and allicin are two components present in garlic which are responsible for garlic's anti-inflammatory properties.(Son, Mo et al. 2006; Keophiphath, Priem et al. 2009) Cellular and animal studies have established the anti-inflammatory effects of garlic by significantly reducing levels of IL-6 and fibrinogen,(Gorinstein, Leontowicz et al. 2006; Son, Mo et al. 2006; Keophiphath, Priem et al. 2009) however in one of the few human intervention studies conducted using garlic powder as one of the interventions no beneficial effects were observed on inflammatory markers (CRP, TNF-a) in the garlic powder treated. (van Doorn, Espirito Santo et al. 2006) More conclusive results have to obtain in human studies to understand the true effect of garlic.

Tea is one of the few food items that have been studied extensively. Green tea and black tea are the two most studied forms of tea. Epicatechin and epigallocatechin-3-gallate (EGCG) are the two important polyphenol components that are responsible for the anti-inflammatory effects. Many cellular and animal studies have shown EGCG to have an anti-inflammatory effect by reducing the cellular expression of cytokines. In a study conducted by Li et al., EGCG inhibited interleukin-6-induced C-reactive protein production in macrophages ,(Li, Liu et al. 2012) in another study conducted by Lu et al., green tea reduced the activity of cyclooxygenase-2 in non-small cell lung cancer cells, (Lu, Jin et al. 2012) EGCG reduced levels of sebum, a chemical responsible for acne, in study conducted on human sebocytes there suggesting a possible protective role of green tea against acne.(Yoon, Kwon et al. 2013) In a study conducted in rats, green tea extract significantly reduced the levels of CRP.(Bornhoeft, Castaneda et al. 2012) Polymeric black tea polyphenols inhibited chemical carcinogenesis on mice skin.(Patel, Krishnan et

al. 2008) In a cross-sectional study conducted by Rebello et al., green tea showed a significant anti-inflammatory association with CRP (Rebello, Chen et al. 2011) whereas in another study conducted in China, no significant association was seen between green tea and CRP.(Villegas, Xiang et al. 2012) No significant associations have been observed in clinical trials. (de Maat, Pijl et al. 2000; Lee, Min et al. 2005; Sung, Min et al. 2005; Ryu, Lee et al. 2006)

Nutrients and Food Constituents

There are several nutrients and food constituents that exert anti-inflammatory effects like fiber, vitamins, magnesium, zinc and flavanoids; and there are also nutrients and food constituents that exert pro-inflammatory effects like protein, carbohydrates, saturated fat, and trans-fat.

There is an ever increasing body of work showing the importance of fiber in protection against chronic inflammation and cancers. Fiber intake has consistently been shown to decrease levels of CRP, (King, Egan et al. 2003; Ajani, Ford et al. 2004; Bo, Durazzo et al. 2006; Ma, Griffith et al. 2006; King, Egan et al. 2007) homocysteine, (Mietus-Snyder, Shigenaga et al. 2012) IL-6 (Ma, Hebert et al. 2008) and tissue plasminogen activator.(Wannamethee, Whincup et al. 2009) Also, in a prospective cohort study conducted on breast cancer survivors dietary fiber significantly reduced levels of CRP(Villasenor, Ambs et al. 2011) another study found a significant inverse relationship between fiber intake and levels of CRP and diabetes.(Wannamethee, Whincup et al. 2009) Dr Ma et al., in the Women's Health Initiative have observed inversed association between dietary fiber and IL-6 and TNF-a, but there was no association with CRP.(Ma, Hebert et al. 2008) Apart from inflammation studies have

shown that fiber is strongly associated with decrease in cancer and cancer related mortality. In a case control study conducted in Germany, authors found significant inverse association between fiber and post-menopausal breast cancer ,(Zaineddin, Buck et al. 2012) in a cohort study conducted in Europe significant protective effect were observed between fiber and all cause mortality and mortality associated with smoking related cancers, (Chuang, Norat et al. 2012) in another study conducted in Denmark, no association was seen between dietary fiber and endometrial cancer. (Aarestrup, Kyro et al. 2012) These findings provide evidence that fiber protects against chronic inflammation.

Effect of fat on inflammation has been researched in many different ways. Some researchers have looked at the association between total fat and inflammation and chronic diseases. Most studies looking at this have observed null associations while some have shown total fat to be pro-inflammatory and none have shown total fat to have an inverse association. All human studied have shown null and pro-inflammatory effects. (Bertran, Camps et al. 2005; Aeberli, Molinari et al. 2006; Koren, Purnell et al. 2006; Esposito, Ciotola et al. 2007; Poppitt, Keogh et al. 2008) In one case control study total dietary fat was found to have a significant positive association between complement C3 which is cardiometabolic risk factor, (Phillips, Kesse-Guyot et al. 2012) another case control study showed total fat to significantly increase levels of IL-6 but not CRP. (Pietraszek, Gregersen et al. 2011) Total dietary fat has also been shown to significantly increase the incidence of ovarian cancer, (Blank, Wentzensen et al. 2012) a couple of cohort studies have shown no effect of total dietary fat on breast cancer. (Zhang, Ho et al. 2011; Park, Kolonel et al. 2012) Researchers have looked at the association between components of

total fat and inflammation. The major anti-inflammatory component of total is omega-3 polyunsaturated fatty acids (PUFA) which is rich in fish. Studies have found high intake of omega-3 fatty acids to significantly reduce levels of inflammatory markers like CRP, IL-6 and TNF- α . (Lopez-Garcia, Schulze et al. 2004; Zhao, Etherton et al. 2004; Zampelas, Panagiotakos et al. 2005; Ferrucci, Cherubini et al. 2006; Niu, Hozawa et al. 2006; Murakami, Sasaki et al. 2008; Tsitouras, Gucciardo et al. 2008; Poudel-Tandukar, Nanri et al. 2009; Turunen, Jula et al. 2013) A cohort study and a case control study have observed no effect of omega-3 on breast cancer risk. (Thiebaut, Chajes et al. 2009; Chajes, Torres-Mejia et al. 2012) The anti-inflammatory effects of omega-6 are weaker than those of omega-3 with many studies showing no effect between omega-6 and CRP, IL-1 β , IL-6, or TNF- α . (Bemelmans, Lefrandt et al. 2004; Fredrikson, Hedblad et al. 2004; Lopez-Garcia, Schulze et al. 2004; Arya, Isharwal et al. 2006; Zhao, Etherton et al. 2007) In a case control study omega-6 was shown to significantly increase the risk of breast cancer, (Chajes, Torres-Mejia et al. 2012) however in another case-control study omega-6 significantly reduced the risk of ovarian cancer. (Ibiebele, Nagle et al. 2012) Cross-sectional epidemiologic studies looking at the association between inflammation and saturated fat intake have shown mixed results, but hint at a possible pro-inflammatory effect. Studies have shown saturated fat to have mainly a pro-inflammatory effect (King, Egan et al. 2003; Lennie, Chung et al. 2005; Aeberli, Molinari et al. 2006; Arya, Isharwal et al. 2006) whereas in some studies no significant associations have been observed. (Baer, Judd et al. 2004; Bertran, Camps et al. 2005; Diaz, Mainous et al. 2005; Klein-Platat, Draï et al. 2005; Ghayour-Mobarhan, Yaghootkar et al. 2007) Trans fat is the main pro-inflammatory component of fat, and

consistent results from both cross-sectional and clinical trial studies, has shown trans-fat be positively associated with inflammation. (Baer, Judd et al. 2004; Mozaffarian, Rimm et al. 2004; Lennie, Chung et al. 2005; Lopez-Garcia, Schulze et al. 2005) In the prospective REGARDS study trans fat was seen to be significantly associated with all cause mortality (Kiage, Merrill et al. 2013) and in another cross-sectional study in Iran, trans fat was responsible for a significant proportion of CHDs.(Mozaffarian, Abdollahi et al. 2007)

There have been varying results with carbohydrates and inflammation in humans and most of the human studies that are conducted involves exercise as an important component of study design. One clinical trials showed an significant inverse association between carbohydrate intake inflammation indicating that it could be anti-inflammatory,(Robson-Ansley, Walshe et al. 2011) however another clinical trial showed that carbohydrate intake had no effect on the levels of inflammatory markers (Miyamoto, Rashid Qureshi et al. 2011)and another study showed carbohydrate to be strongly pro-inflammatory as evidenced by the significant increase in the levels of inflammatory markers.(Depner, Kirwan et al. 2010) (Wood, Volek et al. 2006; Forsythe, Phinney et al. 2008) Not many studies have been conducted looking at association between carbohydrate intake and health outcomes like cancer, a study conducted in Brazil observed an significant positive association between carbohydrate intake and thyroid cancer, (Marcello, Sampaio et al. 2012), another study by Fung et al., observed significant inverse association between vegetable based low carbohydrate scores and ER- breast cancer (Fung, Hu et al. 2011)and a cohort study in Europe found not

significant association between carbohydrate intake CVD associated mortality. (Burger, Beulens et al. 2012)

As with carbohydrates differing results have been seen with protein intake and inflammation, many studies have not found a significant association between intake of protein and levels of pro-inflammatory markers.(Hung, Chertow et al. 2002; Bertran, Camps et al. 2005; Bossola, Muscaritoli et al. 2005; Arya, Isharwal et al. 2006; Clifton, Keogh et al. 2008) A clinical trial showed a significant inverse association between soy protein and CRP compared to the control group. (Azadbakht, Atabak et al. 2008) Similarly studies with protein intake and cancer has shown mixed results, while a few studies have shown a positive association between protein intake and cancer,(Chow, Gridley et al. 1994; Sieri, Krogh et al. 2002) lately studies have shown either no association or inverse association between protein intake and cancer.(Williams, Satia et al. 2010)

Alcohol intake has varying effects on inflammation at different levels, alcohol consumption at moderate levels was found to be associated with lower levels of inflammation.(Imhof, Froehlich et al. 2001; Sierksma, van der Gaag et al. 2002; Avellone, Di Garbo et al. 2006) No association was found between alcohol consumption and levels of inflammatory markers in another study.(Lu, Solomon et al. 2010) Evidence from epidemiologic studies shows an anti-inflammatory effect of moderate alcohol intake and a possible pro-inflammatory effect of excessive intake. Moderate alcohol consumption was associated with a significant decrease in the risk of colorectal cancer in the Mediterranean population,(Kontou, Psaltopoulou et al. 2012) another case control

study in France showed inverse association between moderate alcohol intake and breast cancer. (Bessaoud and Daures 2008)

Micronutrients which include vitamins and minerals play a vital role in fighting against inflammation and protecting against chronic diseases. Most epidemiologic studies have consistently found significant inverse associations between serum Vitamin A and inflammatory markers.(Curran, Sattar et al. 2000; Koyanagi, Kuffo et al. 2004; Bertran, Camps et al. 2005; Kongsbak, Wahed et al. 2006; Aeberli, Biebinger et al. 2007)

However a study in Brazil found no significant correlation between retinol and CRP (Carmem-Costa-do-Nascimento, Cristhine-Porteus-de-Lima et al. 2011) Clinical studies looking at Vitamin A intake and inflammation have also consistently found an anti-inflammatory effect.(Aukrust, Muller et al. 2000; Cusick, Tielsch et al. 2005; Cox, Arthur et al. 2006) A case control study in South Korea observed significant inverse association between vitamin A and cervical cancer ,(Kim, Kim et al. 2010) in a prospective study conducted in Japan, vitamin A intake was found to have an inverse association with gastric cancer.(Miyazaki, Doi et al. 2012)

B group of vitamins have been found to have strong anti-inflammatory properties and hence they have been studied extensively. Studies looking at folate intake and inflammation have observed no significant association. (Folsom, Desvarieux et al. 2003) (Mangoni, Arya et al. 2003; Gunter, Stolzenberg-Solomon et al. 2006) However a study by Solini *et al.* found significant inverse association between folate supplementation and CRP levels but there was not effect seen on IL-6 levels. (Solini, Santini et al. 2006) Researchers found a significant inverse association between folate intake and colorectal cancer (CRC) (Razzak, Oxentenko et al. 2012) and inverse association was observed

between folate intake deaths from breast cancer in the Swedish Mammogram study, (Harris, Bergkvist et al. 2012) however in a clinical trial conducted by Cole et al., significant association was observed between folic acid and colorectal adenomas. (Cole, Baron et al. 2007) Pyridoxal 5'phosphate (PLP) is the active form of vitamin B₆. Several studies have observed significant inverse associations between PLP and. (Lee, Li et al. 2009) (Friso, Jacques et al. 2001; Eley, Sive et al. 2002; Friedman, Hunsicker et al. 2004; Friso, Girelli et al. 2004; Gori, Sofi et al. 2006) A prospective cohort study, by Lee *et al.*, found slightly inverse correlation between folate intake and inflammatory cytokines like CRP, TNF- α and IL-6. (Lee, Li et al. 2009) Inconsistent results have been found for vitamin B₆ among different study designs. Inverse association was seen between vitamin B₆ and CRP in the control groups, however not effect was seen in the group with coronary heart disease, (Cheng, Lin et al. 2008) significant inverse associations were seen between PLP and colorectal cancer in the Physician's Health study. (Lee, Li et al. 2009) Among other B vitamins, cobalamin has been shown to have an anti-inflammatory effect in some studies, (Anwar, Gueant et al. 2001; Peracchi, Bamonti Catena et al. 2001) pro-inflammatory effect in some, (Bolaman, Kadikoylu et al. 2003; Folsom, Desvarieux et al. 2003; Liappas, Nicolaou et al. 2007) and no effect in some. (Leeb, Witzmann et al. 1995; Friso, Jacques et al. 2001; Eley, Sive et al. 2002; Friedman, Hunsicker et al. 2004; Bertran, Camps et al. 2005) Not many studies have looked at the inflammatory effect of thiamin, riboflavin and niacin on humans. More research needs to be done looking at the inflammatory effects of these vitamins.

Vitamin C (ascorbic acid) has been shown to play a key role in controlling inflammation. (Mah, Matos et al. 2011) Most of the studies looking at this association has

been cross-sectional and most of them have observed an inverse association.(Zhang, Liu et al. 2011) (Jacobsson, Lindgarde et al. 1990; Ford, Liu et al. 2003; Mayland, Allen et al. 2004; Humenikova and Gates 2005; Boekholdt, Meuwese et al. 2006) A cross-sectional study conducted on dialysis patients observed significant inverse association between plasma Vitamin C and CRP.(Zhang, Liu et al. 2011) Among clinical trials, however, results mainly show no effect of Vitamin C supplementation on levels of inflammation.(Upritchard, Sutherland et al. 2000; Tousoulis, Antoniadis et al. 2003; Antoniadis, Tousoulis et al. 2004; Fumeron, Nguyen-Khoa et al. 2005; Bo, Ciccone et al. 2007) A clinical trial conducted on patients with atrophic gastritis in Japan showed no association between Vitamin C and CRP,(Ma, Sasazuki et al. 2013) another trial conducted among patients with prostate cancer saw significant reduction in the levels of inflammatory markers with administration of intravenous Vitamin C.(Mikrova, Casciari et al. 2012) Although these results seem to differ among study design, no epidemiologic study has shown a pro-inflammatory effect of Vitamin C. In case control study in Japan no association was observed between Vitamin C intake and colorectal cancer, (Wang, Joshi et al. 2012) in a nested case control study in UK no association was seen between Vitamin C intake and breast cancer (Hutchinson, Lentjes et al. 2012) and similar findings were observed in a case control study among Hispanics (Wang, Baumgartner et al. 2009).

Studies assessing the effect of vitamin D intake on levels of inflammation have shown mixed results. A clinical trial by Sokol et al., found no association between dietary intake of vitamin D and CRP and IL-6. (Sokol, Srinivas et al. 2012) In another case control study conducted among HIV infected patients no association was observed between vitamin D and inflammatory markers. (Eckard, Judd et al. 2012) In a clinical

trial conducted by Grossmann et al., on patients with cystic fibrosis, there was significant reduction in the levels of TNF- α and IL-6 in the vitamin D treatment group but no effect was seen on IL-1 β and IL-10. (Grossmann, Zughaier et al. 2012) Many studies have looked at the association between vitamin D and prostate cancer. A positive association was seen between vitamin D and prostate cancer in a case control study in Norway, (Meyer, Robsahm et al. 2013) in another case control study which was a sub study of PLCO trial, no significant association was observed between serum vitamin D and prostate cancer, (Ahn, Peters et al. 2008) vitamin D has also been shown to be associated with skin cancer in a prospective study in Australia. (van der Pols, Russell et al. 2013) In a study looking at association between vitamin D intake and aggressive breast cancer, women with aggressive breast cancer had significantly lower levels of 25-OH vitamin D. (Peppone, Rickles et al. 2012)

Vitamin E exists in several forms, alpha-tocopherol, gamma-tocopherol and delta-tocopherol and out of this alpha-tocopherol is most associated with inflammation and diseases. Studies have found significant inverse associations between vitamin E and CRP, IL-1 β , IL-6, and TNF- α , (Devaraj, Li et al. 1996; van Tits, Demacker et al. 2000; van Herpen-Broekmans, Klopping-Ketelaars et al. 2004; Bertran, Camps et al. 2005; Gunter, Stolzenberg-Solomon et al. 2006; Garelnabi, Veledar et al. 2012) however several studies have found no association. (Ford, Liu et al. 2003; Mayland, Allen et al. 2004; Bertran, Camps et al. 2005; Chang, Chen et al. 2005; Aeberli, Molinari et al. 2006) A case control study in UK found no association between circulating vitamin E and prostate cancer, (Gilbert, Metcalfe et al. 2012) similar finding was observed in another case control study in Japan (Wang, Joshi et al. 2012) and in a prospective study conducted by Pocobelli

etal., vitamin E was found to significantly reduce CVD mortality but no association was observed with cancer mortality (Pocobelli, Peters et al. 2009) More research has to be done to confirm the anti-inflammatory potential of vitamin E.

Epidemiologic studies consistently show significant inverse associations between serum β -carotene and pro-inflammatory markers like CRP and IL-6.(Curran, Sattar et al. 2000; Kritchevsky, Bush et al. 2000; Erlinger, Guallar et al. 2001; Ford, Liu et al. 2003; Chang, Chen et al. 2005; Helmersson, Arnlov et al. 2009; Muzakova, Kand'ar et al. 2010) In a case control study by Dr Muzokova et al., β -carotene was inversely correlated with IL-6 in patients with coronary heart disease.(Muzakova, Kand'ar et al. 2010) In the Kuopio Ischaemic Heart Disease Risk Factor study men in the highest tertile of serum β -carotene had 2.3 times higher risk of getting prostate cancer than men in the lowest tertile of serum β -carotene,(Karppi, Kurl et al. 2012) in the ATBC study no association was found between β -carotene and lung cancer (1994) and significant inverse association was observed between β -carotene and cervical cancer in a case control study in South Korea.(Kim, Kim et al. 2010)

Minerals also form a major component of micronutrient which have significant role in protecting the body against inflammation. Four minerals have gained a lot interest in the past for their role in preventing inflammation and these are magnesium, zinc, selenium and iron and most of the studies have been done on cell lines and animals. Various human studies have shown results indicating significant anit-inflammatory effects of magnesium.(King, Mainous et al. 2005; Song, Ridker et al. 2005; Bo, Durazzo et al. 2006; Rodriguez-Moran and Guerrero-Romero 2007; Song, Li et al. 2007; Fein, Suda et al. 2010) A study by Fein et al., in patients undergoing haemodialysis showed

magnesium to significantly inversely correlated to CRP levels, (Fein, Suda et al. 2010) in 20 years prospective study conducted by Kim et al., magnesium intake was significantly inversely associated with hs-CRP, IL-6 and fibrinogen (Kim, Xun et al. 2010) another study found that magnesium is inversely associated with levels of CRP, but not with IL-6. (Song, Li et al. 2007) No significant association was found between magnesium and colorectal cancer in a case control study conducted by Wark et al., (Wark, Lau et al. 2012) similarly no association was observed between magnesium and any cancer and cancer related mortality in EPIC-Heidelberg study. (Li, Kaaks et al. 2011)

Studies looking at zinc and inflammation have shown mixed effects. (Strand, Adhikari et al. 2004; Finamore, Devirgiliis et al. 2005; Kongsbak, Wahed et al. 2006; Karyadi, Dolmans et al. 2007) Cross-sectional studies mainly show no association between serum zinc and CRP or IL-6. (Koyanagi, Kuffo et al. 2004; Mayland, Allen et al. 2004; Ghayour-Mobarhan, Taylor et al. 2005; Droke, Kennedy et al. 2006; Walston, Xue et al. 2006) In a prospective study conducted in Japan no significant inverse association was found between zinc and colorectal cancer, (Hara, Sasazuki et al. 2012) in the Nurses' Health Study and Health Professionals Follow-up Study people in the highest quintile of zinc intake had significantly lower risk of developing rectal cancer compared to those in the lowest quintile of zinc intake, however not associations were observed for colorectal cancer and colon cancer. (Zhang, Giovannucci et al. 2011)

Flavonoids are polyphenolic compounds that are broadly classified in to 5 groups: Isoflavones, Flavones, Flavan-3-ol, Flavanones, Anthocyanidins and Flavanol. Most studies have been conducted on animals and tissues and a lot of them have shown flavonoids to be anti-inflammatory. (Chen and Anderson 2001; Mastuda, Morikawa et al.

2002; Blonska, Czuba et al. 2003; Gottstein, Ewins et al. 2003; Suh, Koh et al. 2003; Blonska, Bronikowska et al. 2004; Kowalski, Samojedny et al. 2005; Park, Kim et al. 2005; Comalada, Ballester et al. 2006; Chen, Peng et al. 2007; Choi 2007; Chrzan and Bradford 2007; Garcia-Mediavilla, Crespo et al. 2007; Gutierrez-Venegas, Jimenez-Estrada et al. 2007) Very few studies have been conducted on humans and most of the have found no association between flavonoids and inflammatory markers.(D'Anna, Baviera et al. 2005; Yildiz, Kumru et al. 2005; Greany, Nettleton et al. 2008) However quite a few studies have been conducted looking at the effect of flavonoids on on health outcomes in humans, in a case control study conducted by Christensen et al., total flavonoid , anthocyanidin, isoflavone, flavan-3-ol, flavaonone and flavanol intake have been shown to significantly reduce the risk of lung cancer, (Christensen, Naidu et al. 2012) in a prospective study conducted by Akhter et al., in Japan people in the highest quartile group of isoflavone consumption had lower risk of developing cancer of proximal colon than people in the lowest quartile group,(Akhter, Inoue et al. 2008) in the Netherlands Cohort study no significant association was found between flavones and flavanol and colorectal cancer(Simons, Hughes et al. 2009) and in significant inverse association was observed between a specific plasma isoflavone called diadezein and prostate cancer in the EPIC study.(Travis, Spencer et al. 2009)

Dietary Inflammatory Index (Cavicchia, Steck et al. 2009; Shivappa 2013; Shivappa 2013)

Overview

The original DII was developed to quantify the overall effect of diet on inflammatory potential.(Cavicchia, Steck et al. 2009) At that time 2700 articles

published through 2007 were screened, and 929 were read and scored in formulating the index.(Ockene, Chiriboga et al. 2004) In the original DII, literature review-based scores were multiplied by individuals' actual intakes of food parameters, with no attempt to relate to any external standard of intake. One major issue with this index was that this approach was sensitive to the units of measurement. For example, μg and mg differ by three orders of magnitude and some parameters, such as vitamin A and b-carotene, had to be divided by 100 and others, such as omega-3 and omega-6 fatty acids, multiplied by 10 in order to place them in a "reasonable" range so as not to over- or under-estimate their influence on the overall score.

The new DII is improved in a number of ways. First, an improved scoring system has been applied to the 45 "food parameters," consisting of whole foods, nutrients and other bioactive compounds derived from a much larger literature review. Second, 11 food consumption data sets from around the world were identified that represent a range of human dietary intakes that serve as the "referent" population database to provide comparative consumption data for these 45 food parameters.(McLennan W. 1995; Baborun, Luximon-Ramma et al. 1996; Pan, Kao et al. 1999; Health. 1999.; Parnell, Wilson et al. 2001; Nakamura, Tajima et al. 2002; Henderson, Bates et al. 2004; Chun, Chung et al. 2007; Barquera, Hernandez-Barrera et al. 2009; Shim YJ 2009; Ferrucci, Daniel et al. 2010; 2011; Knudsen, Gille et al. 2011) Third, a percentile scoring system was devised that serves as the actual values against which individuals' intakes are multiplied in order to derive each individual's DII score.

Literature Review Strategy

Pub Med[®] and Ovid[®] were used to search the National Library of Medicine database from 1950 through 2007 for all peer-reviewed articles published in English that met the criteria of assessing the role of whole foods and dietary constituents on these specific inflammatory markers: interleukin-1beta (IL-1 β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF- α), and c-reactive protein (CRP). (Cavicchia, Steck et al. 2009) After confirming that both search engines produced the same results, a Pub Med[®] search was conducted for all peer-reviewed articles published in English from January 2008 through December 2010 to update the inflammatory effect scores (which includes the weight assigned to the quality of study design and number of articles on each food/constituent-inflammatory marker relationship). In the review of these more recent articles the list of constituents was expanded by 15. The previous (i.e., published in or before 2007) set was then re-reviewed to ensure that the full parameter list applied to the entire dataset.

Based on their established importance in inflammation and, concomitantly, the robustness of the literature concerning them, these inflammatory markers were chosen to be the focus of the search: IL-1 β , IL-4, IL-6, IL-10, TNF- α , and CRP. Multiple variations of each term were used in order to decrease the probability of missing relevant articles. Similarly, variations in the names of food parameters were used to ensure that no appropriate article was missed [i.e., to achieve the goal of full and complete representation]. Next, inflammatory terms were combined using the “or” Boolean Logic option.

Each food parameter was individually combined with the list of inflammatory terms using the “and” option. Based on the abstracts, articles were discarded if they: 1) did not examine ≥ 1 food parameter/inflammatory marker relationship; 2) used the inflammatory marker to stimulate other processes; 3) used a combination of food parameters as the exposure; 4) employed intravenous administration of the food parameter; 5) was published after the year 2010; 6) were reviews (because primary study results were required - though bibliographies were read to ensure that all primary research articles cited in reviews were captured); 7) examined extreme, non-physiologic exposures (such as chronic alcohol exposure, alcohol abuse, or ethanol vapor) or 8) used an analogue of the food parameter. A total of 1943 articles were reviewed and scored.

Scoring Algorithm

One of three possible values was assigned to each article based on the effect of the food parameter on inflammation: “+1” was assigned if the effects were proinflammatory (significantly increased IL-1B, IL-6, TNF- α , or CRP or decreased IL-4 or IL-10); “-1” if the effects were anti-inflammatory (significantly decreased IL-1B, IL-6, TNF, or CRP or increased IL-4 or IL-10) and “0” if the food parameter did not produce any significant change in the inflammatory marker. In some instances, in a single study, food parameters have been shown to have differential effects; i.e., a food parameter could both decrease and increase inflammatory potential by increasing both pro and anti-inflammatory markers or by increasing one pro- (or anti-)inflammatory marker while decreasing another. Previously, to deal with these contradictory results the mean effect was computed. Now they are scored separately, giving “-1” to the article for an anti-

inflammatory effect and a “+1” for a pro inflammatory effect reported in the same article. Full details of the scoring algorithm are available on request.

Calculation of Food Parameter-Specific Raw Inflammatory Effect Scores and Food Parameter-Specific Overall Inflammatory Effect Scores

Articles were first weighted by study characteristics (see **Table 1**).

Using these weighted values, the pro- and anti-inflammatory fractions for each food parameter were calculated (see step 3 in Figure 1). The “food parameter-specific overall inflammatory effect score” was then calculated by: 1) dividing the weighted pro- and anti-inflammatory articles by total weighted number of articles and 2) subtracting the anti-inflammatory fraction from the pro-inflammatory fraction (see **Figure 2** for an example of how the score was calculated for saturated fat). A cut point of 236, the median of the total weighted number of articles across all the food parameters, was chosen to indicate an optimally robust pool of literature. All food parameters with a weighted number of articles ≥ 236 were assigned the full value of the score. Foods and constituents with a weighted number of articles < 236 were adjusted as follows: 1) number of weighted articles was divided by 236; 2) the fraction was then multiplied by the food parameter-specific raw inflammatory effect score, which resulted in the **food parameter specific overall inflammatory effect** score (i.e. for saturated fat: $205/236 = 0.87$; $0.87 * 0.429 = 0.373$).

Example of Method Used for Weighting Results of Research Articles, Dietary Inflammatory Index Development and Testing Study, Columbia, SC, 2011-2. Saturated fat had a total of 35 articles, which resulted in 205 weighted. In step 1, articles were multiplied by assigned weights (see Table 1 and Figure 2). The total anti-inflammatory

and pro-inflammatory weight was divided by the total weight for saturated fat. In step 2, the anti-inflammatory fraction was subtracted from the pro-inflammatory fraction.

Developing a composite database representing a diversity of diet

To avoid the arbitrariness resulting from simply using raw consumption amounts (with arithmetic manipulations needed to regulate influence), as had been done previously, the current DII was standardized to a representative range of dietary intake based on actual human consumption. This was accomplished by constructing a composite database representing a wide range of diets across diverse populations living in a variety of countries in different regions of the world. Authors of articles reporting on data from nutrition surveys were contacted to request access to complete datasets. A total of 11 such datasets were identified. If data for some food parameters were missing, then the means were either calculated from other datasets or taken from articles that published mean values for these missing parameters. For example to obtain the data on turmeric, eugenol, rosemary and thyme-oregano consumption for the US we used the Energy Balance dataset, flavonoid data for Denmark was taken from an article published by Dragsted et al. (Dragsted, Strube et al. 1997). All of these datasets had information on all the major macro and micronutrients, it is mainly in cases of flavonoids and whole food items that data were taken from other sources (in any event < 9% of all data). In rare instances (i.e., for thyme, saffron, isoflavones, eugenol) where we failed to identify a mean consumption value for a particular food parameter for all countries, it was left blank for those countries and the overall mean and standard deviation were calculated from the datasets that had information on that food parameter. Some sources, e.g., for

New Zealand, provided means separately for males and females; in such cases the two values were averaged.

Dietary information was available for the following countries (and sources): 1) USA – NHANES dataset 2007-2008(2011) was used to calculate the means for most of the food parameters. For food parameters such as turmeric, thyme, oregano, rosemary and cloves whose data were not available in NHANES, locally available datasets (e.g., the on-going Energy Balance study(Cavicchia, Steck et al. 2009)) were used to provide data on these parameters. 2) Australia – mean values were taken from National Nutrition Survey report of 1999.(McLennan W. 1995) 3) Bahrain – mean values were taken from “National Nutrition Survey for Adult Bahrainis aged 19 years and above” published in 2002.(Bahorun, Luximon-Ramma et al. 1996) 4) Denmark – means were taken from an article published by Knudsen et al.(Knudsen, Gille et al. 2011) in 2010, which used the data from Danish National Survey of Diet and Physical Activity, and the flavonoid data from an article published by Dragsted et al.(Dragsted, Strube et al. 1997) 5) India – means were calculated from Indian Health Study dataset(Ferrucci, Daniel et al. 2010) and from Mumbai Cohort Study dataset (unpublished results from on-going analyses of Feasibility Study data). 6) Japan – means were taken from National Nutrition Survey Report, 2002,(Nakamura, Tajima et al. 2002) the parameters were in Japanese language; hence help was obtained from a Japanese student to translate it in to English. 7) New Zealand – means were taken from National Nutrition Survey Report of 1997.(Health. 1999.; Parnell, Wilson et al. 2001) 8) Taiwan – means were taken from an article published by Pan et al.,(Pan, Kao et al. 1999) entitled ‘Nutrition and Health Survey in Taiwan (NAHSIT) 1993-1996: Dietary Nutrient Intakes Assessed by 24-Hour Recall.’ 9)

South Korea – mean values were taken from an article published by Shim and Paik entitled ‘Reanalysis of 2007 Korean National Health and Nutrition Examination Survey (2007 KNHANES) Results by CAN-Pro 3.0 Nutrient Database’(Shim YJ 2009) and for some of the food parameters that were missing in the above article, mean values were provided by Dr Sung Kyun Park, at the University of Michigan who has worked extensively with KNHANES datasets. 10) Mexico – means were taken from an article published by Barquera et.al,(Barquera, Hernandez-Barrera et al. 2009) which used the Mexican National Health and Nutrition Survey (2006) data. 11) United Kingdom – means were taken from the 2004 summary report entitled ‘The National Diet & Nutrition Survey: adults aged 19 to 64 years’.(Henderson, Bates et al. 2004) For thyme, oregano and rosemary mean consumption was calculated from the Energy Balance study database(Cavicchia, Steck et al. 2009) (unpublished results available on request) and the standard deviation was calculated from the same dataset based on the consumption among the participants in that study. For eugenol, there were no data on its consumption; hence, its consumption was calculated based on the mean consumption of cloves, i.e., the food source that accounts for 95% of all eugenol consumed. For tea and coffee, for which limited survey data were available, daily intake was calculated from the *per capita* intake in these 11 countries.(Heroux, Janssen et al. 2010; O’Neil, Nicklas et al. 2011)

Because no country had complete data on all 21 flavonoids, they were grouped into six main categories based on their biological mechanisms of action. For example, articles on luteolin and apigenin are grouped under the main group as flavones. This reduced the total number of food parameters to 45. Flavonoid data for U.S. were taken from an article published by Chun et al., in 2007(Chun, Chung et al. 2007) who used the

USDA Flavonoid Database and NHANES 1999-2002 as a referent. For food parameters where data were available only from a single country (e.g., thyme); the standard deviation for that country was used.

Calculation of the Dietary Inflammatory Index (DII)

Calculation of the DII is based on dietary intake data that are then linked to the regionally representative world database that provided a robust estimate of a mean and standard deviation for each parameter (see steps 5 and 6 in Figure 1). These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard mean" from the amount reported and dividing this value by its standard deviation (means and standard deviations for all of the 45 parameters are shown in Table 2). To minimize the effect of "right skewing," this value is converted to a percentile score. To achieve a symmetrical distribution with values centered on "0" (null) and bounded between -1 (maximally anti-inflammatory) and 1 (maximally pro-inflammatory) each percentile score is doubled and then "1" is subtracted.

The centered-percentile value for each food parameter is then multiplied by its respective "Overall food parameter-specific inflammatory effect score" to obtain "food parameter-specific DII score" (step 7 in Figure 1). Finally all of the "food parameter-specific DII scores" are summed to create the "overall DII score" for an individual (step 8 in Figure 1). This approach both "anchors" the individual's exposure to a robust range of dietary patterns in a variety of cultural traditions and obviates completely the problem of non-comparability of units because the z-scores and percentiles are independent of the

units of measurement (i.e., the percentile is the same whether the parameter is expressed in *ug* or *mg*).

Validation(Shivappa 2013)

To perform construct validation of the population-based Dietary Inflammatory Index (DII) using dietary data from two different dietary assessments and serum high-sensitivity C-reactive protein (hs-CRP) as the construct validator; data derived from: 1) three 24-hour dietary recalls (24HR) at baseline and at the end of each subsequent quarter (i.e. up to 15 over a year); and 2) a 7-day dietary recall (7DDR) measured at baseline and then quarterly, from the SEASONS study(Merriam, Ockene et al. 1999) was used. As recommended by the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA), we dichotomized hs-CRP at the level of 3mg/L considering measurements greater than this level at higher cardiovascular disease risk (Pearson, Mensah et al. 2003)and regression analyses were conducted to test the effect of the DII score on serum hs -CRP as dichotomous (≤ 3 mg/L, >3 mg/L), while controlling for important potential confounders.

Participants who had at least one hs-CRP measurement over her/his one-year participation were 495 for 24HR subset and 559 for 7DDR subset. Higher DII scores were associated with values of hs-CRP >3 mg/L (odds ratio=1.08; 95%CI 1.01, 1.16, $p=0.035$ for the 24HR; and odds ratio=1.10; 95%CI 1.02, 1.19, $p=0.015$ for the 7DDR).

All cause mortality, overall cancer mortality and CVDs mortality

Overview

In 2011, the age-adjusted death rate for the United States was 740.6 per 100,000 population.(Miniño 2013)The five major causes of death in the US in 2011 are heart

disease, cancer, chronic lower respiratory diseases, stroke, and accidents which accounted for 62% of all deaths in the United States.(Miniño 2013)

Diet and all cause mortality

In two large cohort studies conducted in US, dietary fiber was found to reduce all cause mortality in people who had suffered from CVD event in the past.(Li, Flint et al. 2014)In the Health Professional Follow Up study, long-term moderate alcohol consumption was inversely associated with all-cause mortality. (Pai, Mukamal et al. 2012)Similarly in a cohort study in Netherlands, long term wine intake was inversely associated with all cause mortality.(Streppel, Ocke et al. 2009)In the Rotterdam study nutrient rich diet score was found to have an inverse association with all cause mortality.(Streppel, Sluik et al. 2014)In the Invecchiare in Chianti prospective study, resveratrol consumption at baseline did not reduce overall mortality.(Semba, Ferrucci et al. 2014)

Inflammation and all cause mortality

Higher levels of baseline CRP levels were significantly associated with increased mortality risk in the REGARDS study.(Suzuki, Voeks et al. 2014)In a prospective study in Brazil among aging subjects higher levels of baseline CRP and B-type natriuretic peptide were independent determinants of all cause mortality.(Beleigoli, Boersma et al. 2013)

Cancer

Overview

There are several types of cancers which affect the body. Following is overview on some common cancers in US. CRC is the third most common cancer among men and

women in United States with The American Cancer Society estimating around 102,480 new cases of colon cancer, 40,340 new cases of rectal cancer and 50,830 deaths from CRC in the year 2013. One in 20 people develop CRC in their lifetime. Because of the improved screening facilities and development of better cure for this cancer, the death rate has come down in the past 20 years. After skin cancer, breast cancer is the most common cancer in women and is the second leading cause of cancer deaths in women after lung cancer deaths. According to the estimates from American Cancer Society, there will be 232,340 new cases of breast cancer and 39,620 deaths due to breast cancer in United States in 2013 which means 1 in 8 women are likely to develop breast cancer at some time in their lives and 1 in 36 women are likely to die due to breast cancer. Because of the increased awareness and better screening facilities breast cancer death rates have been going down. Prostate cancer is the most common type of cancer among American men next skin cancer with 238,590 new cases expected in 2013 and is the second leading cause of cancer death after lung cancer with 29,720 deaths from prostate cancer expected in 2013. 1 in 6 men are expected to get prostate cancer and 1 in 36 men are expected to die because of prostate cancer.

Diet & Cancer

Red meat consumption has inconsistently been associated with a higher risk of CRC and colon adenomas. A number of studies have found an increased risk of CRC or colorectal adenoma among individuals with higher red meat intake. (Hsing, McLaughlin et al. 1998; Levi, Pasche et al. 1999; Breuer-Katschinski, Nemes et al. 2001; Amaral, de Almeida et al. 2002; Le Marchand, Donlon et al. 2002; English, MacInnis et al. 2004; Larsson, Rafter et al. 2005; Norat, Bingham et al. 2005; Ferrucci, Sinha et al. 2009)

Mixed results were found among studies looking at the effect of fish consumption on CRC risk.(Hsing, McLaughlin et al. 1998; Boutron-Ruault, Senesse et al. 1999; English, MacInnis et al. 2004; Larsson, Rafter et al. 2005; Norat, Bingham et al. 2005; Yeh, Hsieh et al. 2005; Hall, Chavarro et al. 2008; Sugawara, Kuriyama et al. 2009) However many of these studies have found fish consumption to significantly protect against CRC.(English, MacInnis et al. 2004; Norat, Bingham et al. 2005; Yeh, Hsieh et al. 2005; Hall, Chavarro et al. 2008) Many micronutrients like folate, vitamin B12, B6, selenium have been found to reduce the risk of colorectal cancer.(Giovannucci, Chen et al. 2003; Laso, Mas et al. 2004; Kune and Watson 2006) Several studies have looked at the effect of diet on breast cancer. (Messina 1999; Sieri, Krogh et al. 2002; Bessaoud and Daures 2008; Sieri, Krogh et al. 2008; Thiebaut, Chajes et al. 2009; Wang, Baumgartner et al. 2009; Linos, Willett et al. 2010; Fung, Hu et al. 2011; Sedlacek, Playdon et al. 2011; Villasenor, Ambs et al. 2011; Zhang, Ho et al. 2011; Chajes, Torres-Mejia et al. 2012; Harris, Bergkvist et al. 2012; Hutchinson, Lentjes et al. 2012; Kim, Noh et al. 2012; Mikirova, Casciari et al. 2012; Park, Kolonel et al. 2012; Peppone, Rickles et al. 2012; Zaineddin, Buck et al. 2012; Kruk and Marchlewicz 2013; Shahril, Sulaiman et al. 2013) Dietary fat has been studied extensively but the results so far have been largely inconclusive. High intake of saturated fat was strongly associated with breast cancer in a case control study conducted in Poland(Kruk and Marchlewicz 2013) but in another prospective study EPIC marginal association was observed (Sieri, Krogh et al. 2008) whereas other studies like multiethnic cohort study no association was observed.(Park, Kolonel et al. 2012) In another study folate intake was seen to improve the survival of women with breast cancer,(Harris, Bergkvist et al. 2012) a study in UK found no

association between vitamin c intake and breast cancer(Hutchinson, Lentjes et al. 2012)and in a case control study in Saudi Arabia, inverse association was observed between serum Vitamin D and breast cancer risk.(Yousef, Jacobs et al. 2013) Various dietary factors exert an effect on prostate cancer, some are pro-inflammatory and some are anti-inflammatory.(Messina 1999; Cross, Peters et al. 2005; Tseng, Breslow et al. 2005; Nimptsch, Rohrmann et al. 2008; Travis, Spencer et al. 2009; Bassett, Severi et al. 2012; Drake, Sonestedt et al. 2012; Williams, Whitley et al. 2012; Meyer, Robsahm et al. 2013; Richman, Kenfield et al. 2013) In a case control study calcium intake was observed to be protective against prostate cancer,(Williams, Whitley et al. 2012) in the EPIC-Heidelberg cohort study no significant association was observed between any form of vitamin K and prostate cancer,(Nimptsch, Rohrmann et al. 2008) strong positive association was seen in the NHANES I follow up study(Tseng, Breslow et al. 2005) and a strong positive association was seen between meat intake and prostate cancer.(Cross, Peters et al. 2005) Isoflavones specifically genistein intake decreased the risk of prostate cancer in the EPIC study.(Travis, Spencer et al. 2009) In the the Kuopio Ischaemic Heart Disease Risk Factor study, beta carotene was positively associated with prostate cancer and no association was observed between alpha-tocopherol and retinol and prostate cancer in the same study.(Karppli, Kurl et al. 2012)

Inflammation and Cancer

Many studies have looked at the association between inflammation and CRC. Most studies conducted used IL-6 or CRP as a marker of inflammation. Studies looking at levels of CRP in relation to CRC have found significant positive associations.(Erlinger,

Platz et al. 2004; Nikiteas, Tzanakis et al. 2005; Gunter, Stolzenberg-Solomon et al. 2006; Otani, Iwasaki et al. 2006) Among the cytokines, IL-6 is most commonly used as a marker of inflammation. IL-6 has been consistently found to be associated with CRC. (Piancatelli, Romano et al. 1999; Belluco, Nitti et al. 2000; Chung and Chang 2003; Maihofner, Charalambous et al. 2003; Nikiteas, Tzanakis et al. 2005) Chung and Chang showed that IL-6 levels were significantly higher among colorectal cancer patients compared to healthy subjects. (Chung and Chang 2003) One study has not found an association between IL-6 and CRC. (Belluco, Olivieri et al. 2003) IL-1 β was found to be positively associated with CRC in two studies. (Piancatelli, Romano et al. 1999; Maihofner, Charalambous et al. 2003) Results from a study published by Nikiteas *et al.* found a significant positive association between TNF- α and CRC. (Nikiteas, Tzanakis et al. 2005)

Overall, it seems that inflammation is associated with CRC. More studies need to be conducted to determine the true temporal sequence. Studies have shown an association between inflammation and breast cancer. (Slattery, Curtin et al. 2007; Pierce, Ballard-Barbash et al. 2009; Onitilo, Engel et al. 2012; Hong, Liu et al. 2013) Women with higher CRP levels have higher risk of developing breast cancer (Onitilo, Engel et al. 2012) and breast cancer survival is inversely associated with CRP levels (Pierce, Ballard-Barbash et al. 2009) and in a case control study in India IL- β is associated with breast cancer; (Pooja, Chaudhary et al. 2012) similar result was seen in a case control study in Southwestern US (Slattery, Curtin et al. 2007). NSAIDs like aspirin has shown to be protect women against breast cancer (Brasky, Bonner et al. 2010) but breast cancer risk was found to be increased in women consuming Ibuprofen. (Brasky, Bonner et al. 2010).

In a case control study, levels of CRP was positively higher in the group with prostate cancer compared to benign prostate hypertrophy.(Kim, Jeon et al. 2013) In a prospective cohort study in Finland, no significant association was seen between CRP and fibrinogen and prostate cancer risk.(Toriola, Laukkanen et al. 2013) Innate immunity and inflammation was seen to play a modest role in the development of prostate cancer(Kazma, Mefford et al. 2012) and in the Melbourne Collaborative Cohort Study higher levels of IL-6 was seen among malignant prostate cancer cases compared to benign cancer cases.(Tindall, Severi et al. 2012)

Cardiovascular Disease (CVD)

Overview

In the United States, more than 80 million people suffer from CVD and an average of about one million Americans die each year (Calabro, Golia et al. 2009; Lloyd-Jones, Adams et al. 2009). Worldwide, CVD is the leading cause of mortality, accounting for about half of the deaths among adults (2008). Cardiovascular disease includes coronary heart disease (CHD) (decreased blood supply to the heart), cerebrovascular disease (decreased blood supply to the brain), and peripheral vascular disease (decreased blood supply to the peripheral vasculature) (Fearon and Faux 2009). CHD is the most common form of CVD and accounts for half of the total CVD cases (2008; Lloyd-Jones, Adams et al. 2009). 20% of deaths in the United States in 2005 were due to CHD (Lloyd-Jones, Adams et al. 2009). A stroke (cerebrovascular accident) results from decreased blood supply to the brain. There are two types of stroke, ischemic and hemorrhagic. An ischemic stroke results from decreased blood supply to the brain due to a clot. A hemorrhagic stroke results from the accumulation of blood around the

brain due to a leak in the blood vessel. In 2005, the age adjusted death rate from stroke in the United States was 46.6 per 100,000 people (Lloyd-Jones, Adams et al. 2009).

Current risk factors for CVD include cholesterol levels (high Low-density lipoproteins, low high-density lipoproteins), high blood pressure, diabetes, smoking, physical inactivity, obesity and diet. As will be discussed below, a number of dietary factors have been associated with CVD. Also, chronic inflammation has been shown to be associated with an increased risk of CVD.

Diet & Cardiovascular Disease

A number of studies have assessed the relationship between CVD risk and dietary patterns, whole foods, food constituents, and nutrients (Mente, de Koning et al. 2009). In the Rotterdam study researchers observed significant reduction in CVD mortality with long term wine consumption. (Streppel, Ocke et al. 2009) Similarly long term alcohol consumption resulted in reduced CVD mortality in the Health Professionals Follow Up study. (Pai, Mukamal et al. 2012) Fruit and vegetables, together and separate, show a protective effect in CHD mortality (Mente, de Koning et al. 2009). A number of studies have found there to be a protective effect of fruit and vegetable intake on the risk of stroke, with between a 27% to 55% decrease in risk among the highest intake compared to the lowest. (Cherubini, Ruggiero et al. 2008)

Light, moderate, and heavy drinking has been shown to protect against CVD. The meta-analysis conducted by Mente *et al.* found a significant protective effect of moderate and heavy alcohol intake on CHD risk compared to abstainers (Mente, de Koning et al. 2009). Results published from the Melbourne Collaborative Cohort Study found that, in men, former drinkers had over double the risk of CVD and CHD compared to life-time

abstainers, but no association for other amounts of intake were found (Harriss, English et al. 2007).

A number of types of fat, such as trans-fatty acids, saturated fat, polyunsaturated fatty acids (PUFA), and monounsaturated fatty acids (MUFA) have significantly been associated with CHD (Hu 2009). Results from the Nurse's health study indicate an increased risk of CHD with increasing trans-fat intake (Oh, Hu et al. 2005). In an age-adjusted model saturated fat was significantly positively associated with CHD risk, but the results were attenuated after controlling for other dietary factors (Oh, Hu et al. 2005). Results from this study also showed a significant inverse association between PUFA intake and CHD risk (Oh, Hu et al. 2005). Clinical trials have shown there to be a protective effect of n-3 PUFA supplementation on CVD outcomes (Lavie, Milani et al. 2009; Mente, de Koning et al. 2009).

Overall, Mente *et al.* conclude that the evidence supports a "strong" causal association for the development of CHD with the Mediterranean dietary pattern, vegetables, nuts, Glycemic index or load, and trans-fatty acids (Mente, de Koning et al. 2009).

Inflammation and Cardiovascular Disease

In the past it was thought that atherosclerosis was only a cholesterol storage disease, but in recent years the scientific community has moved away from this idea (Calabro, Golia et al. 2009). Over the years a large number of studies have consistently shown there to be an association between CVD and chronic inflammation (Mora, Musunuru et al. 2009). Since the first study of CRP and CHD risk was carried out in 1996 (Kuller, Tracy et al. 1996), more than 40 other studies have been conducted

between CRP and CHD (Sarwar, Thompson et al. 2009). A review done by Ridker *et al.* in 2003, found that the highest tertile of hs-CRP is positively associated with cardiovascular death, myocardial infarctions, stroke, and peripheral vascular disease (Ridker 2003). A prospective study and meta-analysis conducted by Danesh *et al.* found a significant odds ratio for CHD of 2.13 (CI=1.38-3.28) among individuals in the highest tertile of CRP compared to the lowest (Danesh, Whincup et al. 2000). CRP has even been shown to predict future cardiovascular events better than LDL cholesterol (Ridker, Rifai et al. 2002). hs-CRP has also been shown to be positively associated with stroke in a number of prospective studies (Musunuru, Kral et al. 2008). However, it still remains unclear whether CRP has a causal role in the development of CHD or it is a correlate of known risk factors and therefore limited to use as a predictive tool (Sarwar, Thompson et al. 2009). It is thought, however, that CRP may contribute to the development of CVD by amplifying inflammation and the immune response and regulating complement activation (Yusuf, Hawken et al. 2004; Calabro, Golia et al. 2009).

IL-6 has also been shown to be associated with CVD. A number of prospective epidemiologic studies have shown associations between IL-6 and CHD (Sarwar, Thompson et al. 2009). A study conducted by Danesh *et al.* in two prospective cohort datasets found that long-term IL-6 levels are significantly positively associated with CHD risk (Danesh, Kaptoge et al. 2008).

A central feature in the process of atherosclerosis leading to plaque rupture and thrombosis is vessel wall inflammation (Rosenson and Koenig 2003). Early on in CVD progression, a chronic inflammatory process is triggered by an endothelial dysfunction (Fearon and Faux 2009). This triggering of inflammation is thought to be due to a

response to injury, possibly from cigarette smoking or hypertension (Pearson, Mensah et al. 2003). Recruited leukocytes secrete pro-inflammatory cytokines that cause an acute-phase reaction (secretion of CRP) (Rosenson and Koenig 2003). It is thought that every step in atherogenesis is characterized by inflammation and believed to involve cytokines (Pearson, Mensah et al. 2003).

Metabolic syndrome (MetSyn)

Overview

Metabolic syndrome (MetSyn) consists of a cluster of several metabolic and physiological abnormalities, including obesity, impaired glucose regulation, dyslipidemia and hypertension. The inflammatory markers are considered emergent risk factors and can be potentially used in the clinical stratification of cardiovascular diseases, establishing prognostic values. (Junqueira, Romeo Filho et al. 2009) As per the analysis conducted on adults population from NHANES 2003-2006, 34% of adults met the criteria for MetSyn which indicated that this disease is widely prevalent in the general population.(Ervin 2009) It has become a subject of paramount interest in both research and clinical medicine, owing to its association with the increased risk of developing type 2 diabetes and atherosclerotic cardiovascular disease (CVD).(Ford 2005) While several theories have been proposed in the etiology and progression of MetSyn, they all tend to point out inflammation as a key factor in the pathogenesis of the disease.(Grundy 2003) Therefore, treating or preventing the progression of this disease through modifications of modifiable life-style factors, such as dietary behaviors is crucial.

Metabolic syndrome and diet

A number of studies have assessed the relationship between MetSyn and diets; inverse association has been observed between diets high in fruits and vegetables and MetSyn. (Esmailzadeh, Kimiagar et al. 2006; Fonseca, Gaio et al. 2012) Mediterranean style diet has been shown to reduce the levels of inflammatory markers among patients with MetSyn. (Esposito, Marfella et al. 2004) In a case control study conducted in France, dietary fat had a strong positive association with MetSyn. (Phillips, Kesse-Guyot et al. 2012) In an intervention study on obese people with MetSyn hypocaloric diet rich in whole grain resulted in a reduction in CVD risk factors and a modest decrease in weight. (Katcher, Legro et al. 2008) Increase magnesium reduced the risk of MetSyn in middle and older US women. (Song, Ridker et al. 2005) Previous research examining the effect of dietary fiber in reducing the risk of MetSyn has shown higher intakes of dietary fiber but not low intakes of saturated fat or cholesterol are related to the MetSyn in adolescents. (Carlson, Eisenmann et al. 2011) In another study in Brazil reduced fiber content was positively associated with MetSyn. (Silva, Steemburgo et al. 2011) However in an intervention trial comparing the effect of high protein weight reducing diet with high carbohydrate, high fiber diet in fat loss and lowering blood pressure among people with MetSyn, better results were seen with high protein weight reducing diet. (Te Morenga, Levers et al. 2011)

Inflammation and MetSyn

Previous research has shown inflammation to be strongly associated with MetSyn. (Grundy 2003; Ridker 2003; Song, Ridker et al. 2005; Giugliano, Ceriello et al. 2006; Azadbakht, Kimiagar et al. 2007; Musunuru, Kral et al. 2008; Galassetti 2012; Musani,

Vasan et al. 2013) In the Jackson Heart study higher levels of CRP was associated with increased incidence of MetSyn(Musani, Vasan et al. 2013)and in another study CRP was associated with MetSyn among middle and older US women.(Song, Ridker et al. 2005) In another study along with obesity and diabetes, inflammation was associated with MetSyn.(Galassetti 2012)Systemic inflammation in terms of levels of CRP was higher in COPD patients with MetSyn compared to those without MetSyn.(Akpinar, Akpinar et al. 2012)In another case control study, increased levels of inflammatory markers like CRP, IL-6 and adiponectin were associated with increased risk of MetSyn.(Chen, Yen et al. 2012)In the Finnish population-based study inflammatory markers like CRP and adiponectin were strongly correlated to all the components of MetSyn(Saltevo, Vanhala et al. 2007)and in a cross-sectional study high levels of adiponectin level and low hs-CRP and IL-1Ra levels were associated with resolution of MetSyn. (Ahonen, Saltevo et al. 2012)In a case control study the presence of MetSyn resulted in increase in hs-CRP levels in people with an observed acute coronary disease event.(Kilic, Jneid et al. 2009)

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CHAPTER 3

Methods

Introduction to the three aims

Dietary Inflammatory Index (DII) will be calculated in the National Health and Nutrition Examination Survey (NHANES) 2005-2010, NHANES III study and the CAN DO intervention study. Aim 1 would look at the predictive ability of DII with C - reactive protein (CRP) as outcome in NHANES 2005-2010 dataset. An additional analysis will be performed with NHANES 2007-2008 dataset where in results with DII and CRP will be compared with Healthy Eating Index-2010 (HEI-2010) and CRP results. Aim 2 would look at the predictive ability of DII with overall mortality, colorectal cancer, breast cancer and prostate cancer specific mortalities in NHANES III study which is linked to death certificates found in the National Death Index (NDI). Aim 3 would look at the effect of DII on the changes with blood pressure, lipid profiles, HBA1_C, hs-CRP, TNF- α , and IL-6 in CAN DO study which is a dietary intervention trial where eligible people with MetSyn were randomized to the high fiber condition or the American Heart Association diet condition. We will also determine if, compared to baseline, six months of a high fiber dietary intervention significantly decreases DII scores relative to an American Heart Association diet.

Aim 1: National Health and Nutrition Examination Survey (NHANES) 2005-2010

Study design

Briefly, the NHANES is a cross-sectional population-based study in which information was collected in two-year cycles using a complex probability design to select participants from various locations and racial/ethnic groups in order to ensure a nationally representative sample of the US population.(CDC 2013) To increase the precision of estimates derived from the survey, adolescents, the elderly, Mexican-Americans, and Blacks are oversampled. The protocol for conduct of the NHANES was approved by the institutional review board of the National Center for Health Statistics, CDC. Informed consent was obtained from all participants.

For this study, 24-hour dietary recall interviews (24HR), CRP, and covariates data were obtained from NHANES 2005-2010 in order to perform a cross-sectional analysis. Data on demographic characteristics were obtained through a self-administered questionnaire. Anthropometric measurements and blood samples were collected, and levels of inflammatory markers were determined.(Rietzschel, De Buyzere et al. 2007) Basic clinical data assessment and routine biochemical assays were performed, as described previously.(Rietzschel, De Buyzere et al. 2007)

Dietary Intake and Dietary Inflammatory Index (DII) (Cavicchia, Steck et al. 2009; Shivappa 2013)

Dietary data in NHANES were collected using 24HR conducted at the mobile examination center (MEC). The dietary interviews were administered by trained staff and

the USDA's Food Surveys Research Group was responsible for the dietary data collection methodology, maintenance of the databases used to code and process the data, and data review and processing. 24HR-derived dietary information was used to calculate DII scores for all subjects, as described in detail elsewhere.(Cavicchia, Steck et al. 2009; Shivappa 2013) Briefly, the dietary data for each participant were first linked to the regionally representative global database that provided a robust estimate of a mean and standard deviation for each of the food parameters (i.e., foods, nutrients, and other food components such as flavonoids) considered,(Shivappa 2013) to derive a z-score, by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing" (a common occurrence with dietary data), this value was then converted to a centered percentile score which ranged from -1 to +1 for each food parameter. This was then multiplied by the respective food parameter inflammatory effect score (derived from a literature review and scoring of 1943 articles) to obtain the subject's food parameter-specific DII score. All of the food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. A description of validation work of the DII score, based on both dietary recalls and a structured questionnaire-7 day dietary record (7DDR) similar to a FFQ, is available elsewhere.(Shivappa 2013) For the current study, data were available for a total of 26 food parameters (carbohydrate, protein, total fat, fiber, cholesterol, saturated fat, mono unsaturated fat, poly unsaturated fat, omega-6 fatty acid, thiamin, riboflavin, vitamin B12, iron, magnesium, zinc, vitamin A and vitamin C). A higher DII score indicates a more pro-inflammatory diet.

Healthy Eating Index-2010 (HEI-2010)- HEI-2010.

The Healthy Eating Index (HEI) was first developed in 1995 to indicate the extent to which an individual's diet adheres to official guidelines described in the United States Department of Agriculture Food Guide Pyramid and was later updated to create versions in 2005 (HEI-2005) and 2010 (HEI-2010). (Kennedy, Ohls et al. 1995; Guenther, Reedy et al. 2008; Guenther, Casavale et al. 2013) The HEI-2010 scores 12 components for a total of 100 points. Six components—total vegetables, “greens and beans” (dark green vegetables and any legumes that are not already counted as protein foods), total fruit, whole fruit, seafood and plant proteins, and total protein foods—are worth 0–5 points; five components—whole grains, low-fat dairy, FA ratio [(PUFA+MUFA): SFA], refined grains, and sodium—are worth 0–10 points; and 1 component—“empty calories” (energy from solid fats, added sugars, and any alcohol in excess of 13 g/1000 kcal)—is worth 0–20 points. All components except for the FA ratio are scored on a density basis (per 1000 kcal or as a percentage of energy). A higher HEI-2010 score indicates a healthier diet.

High Sensitivity-C-Reactive Protein (hs-CRP). Serum CRP was assayed at the University of Washington Medical Center Department of Laboratory Medicine using a Dade Behring Nephelometer II Analyzer system (Dade Behring Diagnostics).

Statistical analysis:

Hs-CRP was log transformed, as values were not normally distributed. As recommended by the CDC and the American Heart Association, we also dichotomized

hs-CRP at the level of 3 mg/L,(Pearson, Mensah et al. 2003) considering measurements greater than this level to place individuals at higher CVD risk.

All statistical analyses were carried out using SAS[®] statistical software package version 9.3 (SAS Institute Inc., Cary, NC). Both dietary indices were categorized by quartiles. Comparisons of baseline characteristics by quartiles of DII were made using χ^2 tests for categorical variables and ANOVA tests for continuous variables. After excluding participants with missing dietary and CRP information, age ≤ 19 years, with calorie intake < 500 and > 5000 kcals/day, CRP ≥ 10 mg/L and missing any of the covariates; there were 12811 subjects with evaluable data, of whom 6371 were men and 6440 were women.

Multivariable analyses were carried out adjusting for total caloric intake, age, sex, body mass index [BMI= weight(kg)/height(m)²], race, education status, blood pressure, insurance, marital status, smoking history, diabetes status, cardiovascular disease status and physical activity. Analyses also were carried out stratified by diabetes status, CVD status and race.

AIM 2: National Health And Nutrition Examination Survey III (NHANES III)

Study

Subjects providing data for this analysis were participants in the NHANES III (1988–1994), which is a nationally representative sample of the civilian, noninstitutionalized US population. Details of the survey design have been reported previously.(1994) The current study was restricted to participants above 19 years of age

at baseline, with complete data on mortality status, diet, and relevant covariates (n = 12,366).

In the NHANES III cohort study, mortality information is derived on the basis of a probabilistic match between NHANES III and the National Death Index records through 31 December 2006 by the National Center for Health Statistics. For overall mortality we included deaths from all causes. For cancer-specific mortality we included deaths from malignant neoplasms which were coded from C00-C97 in the International Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10). For digestive-tract cancers we included malignant neoplasms from the front of the mouth to the rectum and malignant neoplasms of pancreas and hepato-biliary system (ICD-10=C00-C16, C18-C22, C25). For CVD related mortality we used ICD-10=I00-I178.

Dietary information was obtained from an in-person 24HR with the use of a personal computer-based, automated, interactive data collection and coding system that was developed by the University of Minnesota's Nutrition Coordinating Center, and conducted by trained interviewers. 24HR-derived dietary data were used to calculate DII scores for all participants. The DII is based on literature published through 2010 linking diet to inflammation. Developing the DII involved review and scoring nearly 2000 scientific articles on cell culture and laboratory animal experiments, and cross-sectional, longitudinal and intervention trials in humans of diet and six inflammatory markers [i.e., CRP, interleukin (IL)-1 β , IL-4, IL-6, IL-10, and tumor necrosis factor (TNF)- α]. Individual intakes of food parameters on which the DII is based are then compared to a world standard database of dietary intake based on datasets from 11 different regions

worldwide. A complete description of the DII is available elsewhere.(Cavicchia, Steck et al. 2009; Shivappa 2013) Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the world database that provided a robust estimate of a mean and standard deviation for each parameter.(Shivappa 2013) These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing," this value is then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed to create the overall DII score for every participant in the study.(Shivappa 2013)A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, also is available.(Shivappa 2013)

Associations with DII for demographic factors, lifestyle factors, self-reported diabetes mellitus, anthropometric characteristics, and weights and servings of food groups were examined using ANOVA models or χ^2 tests (see Table 1 for specific variables). DII was analyzed both as a continuous variable and by tertiles of exposure in relation to various mortality outcome variables, consisting of all-cause, overall cancer, digestive-tract cancer and CVD-related mortalities. Hazard ratios and 95% confidence intervals (HR; 95% CI) were estimated using Cox proportional hazards regression

models, adjusting only for age in the first model and additionally adjusting for body mass index [BMI = weight (kg)/weight (m)²], smoking status, sex, race, diabetes status, hypertension status, physical activity, and poverty index (PI) in the second model. Physical activity was assessed by questionnaire and coded as the number of moderate to vigorous intensity activities in the past month; PI was used to capture socioeconomic status, the poverty to income ratio is an index of poverty status which is calculated by dividing family income by a poverty threshold specific to family size. The covariates were chosen *a priori* as they were shown previously to be strong risk factors for the outcomes of interest in this cohort. Participants with extreme energy intake values (≤ 500 kcals and ≥ 5000 kcals), with abnormal BMI values (> 50 kg/m²) or PI values (> 10), or who had a history of cancer at baseline were excluded. Energy was not included in the model because energy is a component of the DII. A linear test for trend was conducted by including the median value for each DII tertile as a continuous term into the regression model. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated. Statistical tests were performed using SAS[®] 9.3, (SAS Institute Inc., Cary, NC); all statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

AIM 3: CAN DO study

Study design

Briefly, the CAN DO study is a dietary intervention trial conducted at the University of Massachusetts Medical School (UMMS), Worcester, Massachusetts, USA

from May 2009 to February 2013. The study protocol was approved by the UMMS Institutional Review Board for use of human subjects in medical research and all participants gave informed consent. To be included in the study individuals had to meet at least three of the components of MetSynyn, be non diabetic, have a body mass index (BMI) $>30 \text{ mg/kg}^2$ but $<40 \text{ mg/kg}^2$, and have a fasting blood sugar $\leq 126 \text{ mg/dl}$. In total 240 participants were recruited, deemed to be eligible, and randomized into one of the two dietary interventions: a high-fiber diet or the American Heart Association (AHA) diet. In the high-fiber diet condition, participants received instruction to achieve a daily dietary goal of $\geq 30\text{g}$ fiber intake from a variety of food sources. Participants in AHA diet group were instructed to make dietary changes addressing both macro- and micronutrients as recommended by the AHA 2006 dietary guidelines. There was no control arm in this study.

Data were obtained at baseline on demographic characteristics including age; race/ethnicity, education, marital status, household income, and employment status using a self-administered questionnaire. Anthropometric data and blood were collected at baseline, 6-month and 12-month visits. BMI [$\text{weight}(\text{kg})/\text{height}(\text{m})^2$] was calculated for each time point and was categorized as mild [class I, BMI 30 to <35] or moderate (class II, BMI 35 to 40) obesity. Serum was collected after a 12-h fast and stored at -80°C . To measure insulin, IMMUNLITE 2000 insulin was used, it is a solid-phase, enzyme-labeled chemiluminescent immunometric assay. The SYNCHRON LX System was used to measure glucose; it determines GLUCm concentration by an oxygen rate method employing a Beckman Coulter oxygen electrode. Insulin resistance, assessed by the homeostasis model assessment (HOMA-IR), was calculated as follows: $\text{HOMA-IR} =$

fasting plasma insulin ($\mu\text{U/mL}$) \times fasting plasma glucose (mg/dL)/405.(Matthews, Hosker et al. 1985) Basic clinical data assessment and routine biochemical assays were performed as described previously.(Rietzschel, De Buyzere et al. 2007) In addition, levels of three inflammatory markers were measured: high-sensitive C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).

Dietary Intake(Hoebeeck, Rietzschel et al. 2011) and Dietary Inflammatory Index (DII)(Cavicchia, Steck et al. 2009; Shivappa 2013)

Diet was assessed through three 24-h dietary recalls (24HR) administered by trained registered dietitians at baseline, 3-, 6- and 12-month visits using the Nutritional Data System for Research (NDS-R) software.(Nutrition Coordinating Center) The participants received a food portion visual booklet prior to receiving the assessment calls to facilitate portion size estimation. This 24HR- derived dietary information was used to calculate DII scores for all subjects, as described in detail elsewhere.(Cavicchia, Steck et al. 2009; Shivappa, Steck et al. 2013) Briefly to describe the methods involved in DII calculation, the dietary data for each study participant were first linked to the regionally representative global database that provided a robust estimate of a mean and standard deviation for each of the food parameters (i.e., foods, nutrients, and other food components such as flavonoids) considered,(Shivappa, Steck et al. 2013) to derive a z-score, by subtracting the “standard global mean” from the amount reported and dividing this value by the standard deviation. To minimize the effect of “right skewing” (a common occurrence with dietary data), this value was then converted to a centered percentile score which was then multiplied by the respective food parameter effect score (derived from a literature review and scoring of 1943 articles) to obtain subject’s food

parameter-specific DII score. All of the food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. Data were available from 29 food parameters.

Statistical analysis:

Means and standard deviations of DII were calculated at each time point for both of the intervention groups, and the trend in DII across the time points were plotted using line graphs. Insulin, blood glucose, HOMA-IR, hs-CRP, IL-6 and TNF- α were log transformed as they were not normally distributed. DII was analyzed as both continuous and grouped into tertiles.

All statistical analyses were carried using SAS[®] statistical software package version 9.3 (SAS Institute Inc., Cary, NC). Comparisons of baseline characteristics across tertiles of DII were made using χ^2 tests for categorical variables and ANOVA for continuous variables. . Multivariable analyses were carried out with log transformed metabolic (insulin, glucose and HOMA-IR) and inflammatory biomarkers (CRP, IL-6 and TNF- α) as outcomes.. Sex, race/ethnicity, time-points, high triglycerides, BMI, and intervention group were considered as covariates due to their potential associations with insulin resistance. Linear mixed models with random intercepts were used.

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CHAPTER 4

Association between dietary inflammatory index and C-Reactive Protein in NHANES 2005-2010

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ABSTRACT

Background: Previous research has shown that nutrients and certain food items influence inflammation. However, little is known about associations between diet as a whole and inflammatory markers. **Objective:** In this study, we examine the predictive ability of a 24-hour recall (24HR)-derived dietary inflammatory index (DII) on inflammation. **Method:** Data were obtained from the National Health and Nutritional Examination Survey (NHANES) 2005-2010, a cross-sectional study with a sample size of 16,190 participants representing different regions of the US. DII is a population-based, literature-derived dietary index developed to assess the inflammatory potential of diet. DII and HEI-2010 were calculated from 24-HR derived dietary information and were tested against the inflammatory marker, C-reactive protein (CRP). CRP, when used as a continuous variable, was log transformed as it was not normally distributed. CRP also was categorized based on the recommended cut-off of 3 mg/L. DII and HEI-2010 were categorized by quartiles. Analyses were performed using multivariable logistic and linear regression, adjusting for energy intake, age, sex, BMI, race, education status, blood pressure, insurance, smoking history, marital status, diabetes status, cardiovascular disease status, and physical activity. **Results:** Multivariable analyses revealed CRP to be positively associated with $DII_{\text{Quartile4vs1}}$ [$\beta = 0.19$, 95% confidence interval (95% C.I.) 0.13, 0.24], and $HEI-2010_{\text{Quartile1vs4}}$ ($\beta = 0.15$, 95% C.I. 0.10, 0.20). Similar associations were observed when CRP was categorized (>3 mg/l), $DII_{\text{Quartile4vs1}}$ (OR= 1.38, 95% C.I. 1.27, 1.71), and $HEI-2010_{\text{Quartile1vs4}}$ (OR= 1.31, 95% C.I. 1.12, 1.56). **Conclusion:** The results provide further evidence that the DII is significantly associated with CRP in a population-based sample of participants in the US. Comparatively, the DII has a better predictive

ability of CRP than the HEI-2010. Future studies are warranted to examine the association between the DII and inflammation-related diseases.

Introduction

Acute inflammation, a necessary process of the body's natural response to tissue injury, helps to heal wounds and promote tissue regeneration.(Thun, Henley et al. 2004; Keibel, Singh et al. 2009; Pan, Lai et al. 2009; Warnberg, Gomez-Martinez et al. 2009) A chronic, low-grade inflammatory state results when this process of inflammation is not controlled properly.(Warnberg, Gomez-Martinez et al. 2009) Chronic inflammation has been shown to be associated with cancer (Terzić, Grivennikov et al. 2010; Elinav, Nowarski et al. 2013) and cardiovascular diseases. (Ridker, Rifai et al. 2000; Blake and Ridker 2002; Ridker, Rifai et al. 2002; Pearson, Mensah et al. 2003) Major inflammatory markers that are shown to be elevated in these chronic diseases include IL-6,(Ridker, Rifai et al. 2000) fibrinogen,(Danesh, Collins et al. 1998) high-sensitivity C-reactive protein,(Danesh, Collins et al. 1998) and leukocyte count.(Danesh, Collins et al. 1998)

Dietary factors also have been associated with inflammation. The Western-type diet, which is high in red meat, high-fat dairy products, and refined grains, has been associated with higher levels of CRP, IL-6 and fibrinogen.(King, Egan et al. 2003; Johansson-Persson, Ulmius et al. 2013) On the other hand, the Mediterranean diet, which is high in whole-grains, fruit and green vegetables and fish, and low in red meat and butter, with moderate alcohol and olive oil intake, has been associated with lower levels of inflammation.(Estruch, Martinez-Gonzalez et al. 2006) Diets high in fruits and vegetables have been associated with lower levels of CRP.(Esmailzadeh, Kimiagar et al. 2006) Specific nutrients also have consistently been shown to be associated with lower

levels of inflammation. These include complex carbohydrates,(Kitabchi, McDaniel et al. 2013) omega-3 polyunsaturated fatty acids (PUFA),(Ferrucci, Cherubini et al. 2006) fiber,(Ma, Griffith et al. 2006) moderate alcohol intake,(Avellone, Di Garbo et al. 2006) vitamin E,(Bertran, Camps et al. 2005) vitamin C,(Wannamethee, Lowe et al. 2006) β -carotene,(Erlinger, Guallar et al. 2001) and magnesium.(King, Mainous et al. 2005)

The original dietary inflammatory index (DII) was developed to provide a means for estimating the overall inflammatory potential of the diet.(Cavicchia, Steck et al. 2009; Shivappa 2013) Subsequent to its introduction in 2009, it has been refined in order to reflect the increase in scientific knowledge over the past four years and to improve applicability across a wide range of human populations.(Shivappa 2013)The DII is based upon an extensive literature search incorporating cell culture, animal, and epidemiologic studies of the effect of diet on inflammation. DII scoring is not dependent on subjective evaluation of the diet or recommendations of intake. The DII is not limited to micronutrients and macronutrients, but also incorporates commonly consumed components of the diet including flavonoids, spices, and tea. Previously, the DII has been shown to predict CRP levels(Cavicchia, Steck et al. 2009; Shivappa 2013) in a predominantly European American population. In order to examine whether this association exists in a more diverse population, we used the National Health and Nutrition Examination Survey (NHANES)-2005-2010, to test the main hypothesis that individuals with higher DII scores, indicating a more pro-inflammatory diet, have increased systemic inflammation as shown by increased levels of CRP. We also hypothesize that the associations with CRP are better for DII compared to HEI-2010.

Methods:

Study design

Briefly, the NHANES is a cross-sectional population-based study in which information was collected in two-year cycles using a complex probability design to select participants from various locations and racial/ethnic groups in order to ensure a nationally representative sample of the US population.(CDC 2013) To increase the precision of estimates derived from the survey, adolescents, the elderly, Mexican-Americans, and Blacks are oversampled. The protocol for conduct of the NHANES was approved by the institutional review board of the National Center for Health Statistics, CDC. Informed consent was obtained from all participants.

For this study, 24-hour dietary recall interviews (24HR), CRP, and covariates data were obtained from NHANES 2005-2010 in order to perform a cross-sectional analysis. Data on demographic characteristics were obtained through a self-administered questionnaire. Anthropometric measurements and blood samples were collected, and levels of inflammatory markers were determined.(Rietzschel, De Buyzere et al. 2007) Basic clinical data assessment and routine biochemical assays were performed, as described previously.(Rietzschel, De Buyzere et al. 2007)

Dietary Intake and Dietary Inflammatory Index (DII) (Cavicchia, Steck et al. 2009; Shivappa 2013)

Dietary data in NHANES were collected using 24HR conducted at the mobile examination center (MEC). The dietary interviews were administered by trained staff and the USDA's Food Surveys Research Group was responsible for the dietary data

collection methodology, maintenance of the databases used to code and process the data, and data review and processing. 24HR-derived dietary information was used to calculate DII scores for all subjects, as described in detail elsewhere.(Cavicchia, Steck et al. 2009; Shivappa 2013) Briefly, the dietary data for each participant were first linked to the regionally representative global database that provided a robust estimate of a mean and standard deviation for each of the food parameters (i.e., foods, nutrients, and other food components such as flavonoids) considered,(Shivappa 2013) to derive a z-score, by subtracting the “standard global mean” from the amount reported and dividing this value by the standard deviation. To minimize the effect of “right skewing” (a common occurrence with dietary data), this value was then converted to a centered percentile score which ranged from -1 to +1 for each food parameter. This was then multiplied by the respective food parameter inflammatory effect score (derived from a literature review and scoring of 1943 articles) to obtain the subject’s food parameter-specific DII score. All of the food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. A description of validation work of the DII score, based on both dietary recalls and a structured questionnaire-7 day dietary record (7DDR) similar to a FFQ, is available elsewhere.(Shivappa 2013) For the current study, data were available for a total of 26 food parameters (carbohydrate, protein, total fat, fiber, cholesterol, saturated fat, mono unsaturated fat, poly unsaturated fat, omega-6 fatty acid, thiamin, riboflavin, vitamin B12, iron, magnesium, zinc, vitamin A and vitamin C). A higher DII score indicates a more pro-inflammatory diet.

Healthy Eating Index-2010 (HEI-2010)- HEI-2010 The Healthy Eating Index (HEI) was first developed in 1995 to indicate the extent to which an individual’s diet

adheres to official guidelines described in the United States Department of Agriculture Food Guide Pyramid and was later updated to create versions in 2005 (HEI-2005) and 2010 (HEI-2010). (Kennedy, Ohls et al. 1995; Guenther, Reedy et al. 2008; Guenther, Casavale et al. 2013) The HEI-2010 scores 12 components for a total of 100 points. Six components—total vegetables, “greens and beans” (dark green vegetables and any legumes that are not already counted as protein foods), total fruit, whole fruit, seafood and plant proteins, and total protein foods—are worth 0–5 points; five components—whole grains, low-fat dairy, FA ratio [(PUFA+MUFA): SFA], refined grains, and sodium—are worth 0–10 points; and 1 component—“empty calories” (energy from solid fats, added sugars, and any alcohol in excess of 13 g/1000 kcal)—is worth 0–20 points. All components except for the FA ratio are scored on a density basis (per 1000 kcal or as a percentage of energy). A higher HEI-2010 score indicates a healthier diet.

High Sensitivity-C-Reactive Protein (hs-CRP). Serum CRP was assayed at the University of Washington Medical Center Department of Laboratory Medicine using a Dade Behring Nephelometer II Analyzer system (Dade Behring Diagnostics).

Hs-CRP was log transformed, as values were not normally distributed. As recommended by the CDC and the American Heart Association, we also dichotomized hs-CRP at the level of 3 mg/L, (Pearson, Mensah et al. 2003) considering measurements greater than this level to place individuals at higher CVD risk.

All statistical analyses were carried out using SAS[®] statistical software package version 9.3 (SAS Institute Inc., Cary, NC). Both dietary indices were categorized by quartiles. Comparisons of baseline characteristics by quartiles of DII were made using χ^2 tests for categorical variables and ANOVA tests for continuous variables. After excluding

participants with missing dietary and CRP information, age ≤ 19 years, with calorie intake < 500 and > 5000 kcals/day, CRP ≥ 10 mg/L and missing any of the covariates; there were 12811 subjects with evaluable data, of whom 6371 were men and 6440 were women.

Multivariable analyses were carried out adjusting for total caloric intake, age, sex, body mass index [BMI= weight(kg)/height(m)²], race, education status, blood pressure, insurance, marital status, smoking history, diabetes status, cardiovascular disease status and physical activity. Analyses also were carried out stratified by diabetes status, CVD status and race.

Results:

Values of the DII ranged from -4.98 to 4.95 and values of the HEI-2010 ranged from 0 to 96.01. The DII was negatively correlated with HEI-2010 ($\rho = -0.52$, p -value < 0.0001); 49.5% of participants in quartile 4 of DII (most pro-inflammatory) were present in quartile 1 of HEI-2010 (least healthy quartile for HEI-2010), similarly 49.1 % of participants in quartile 1 of DII (most anti-inflammatory quartile of DII) were present in quartile 4 of HEI-2010. Males had significantly lower mean DII (i.e., less inflammatory diet) compared to females (0.64 ± 1.78 vs 1.23 ± 1.76).

Table 1 shows the characteristics of the participants across quartiles of DII scores. Both BMI and hs-CRP increased with increasing DII scores. Individuals in DII quartile 4 were more likely to be males and more likely to have less education, be non Hispanic Black, lack insurance, have history of diabetes and hypertension compared to those in DII quartile 1.

Analysis of CRP as a continuous variable

Both indices were categorized into quartiles; for comparative purposes quartile 4 of HEI-2010 was used as the reference group. Analyses adjusted for energy intake, age, sex, BMI, race, education status, blood pressure, insurance, smoking history, marital status and physical activity revealed significantly positive association between log hs-CRP and both DII and HEI-2010. The DII showed slightly stronger linear association [DII_{Quartile 4vs1}, β =0.19, 95%C.I. 0.13, 0.24, p-trend=<0.0001; HEI-2010_{Quartile 1vs4}, β =0.15, 95%C.I. 0.10, 0.20, p-trend=<0.0001 (Table 2)]. When stratified by diabetes and CVD status, positive associations were seen for both the indices only in the non diabetic group (DII_{Quartile 4vs1}, β =0.21, 95%C.I. 0.15, 0.27, p-trend=<0.0001; HEI-2010_{Quartile 1vs4}, β =0.17, 95%C.I. 0.11, 0.22, p-trend=<0.0001) whereas a positive association was observed for DII but not for HEI-2010 in the CVD group (DII_{Quartile 4vs1}, β =0.22, 95%C.I. 0.05, 0.39, p-trend=0.007; HEI-2010_{Quartile 1vs4}, β =0.15, 95%C.I. -0.003, 0.30, p-trend=0.04) even though the trend is significant and for both the indices in non CVD group (DII_{Quartile 4vs1}, β =0.19, 95%C.I. 0.13, 0.25, p-trend=<0.0001; HEI-2010_{Quartile 1vs4}, β =0.15, 95%C.I. 0.10, 0.20, p-trend=<0.0001) When stratified by race both DII and HEI-2010 showed significant positive association with hs-CRP in the non-Hispanic white group (DII_{Quartile 4vs1}, β =0.22, 95%C.I. 0.14, 0.30, p-trend=<0.0001; HEI-2010_{Quartile 1vs4}, β =0.19, 95%C.I. 0.12, 0.26, p-trend=<0.0001); (Table 3).

Analysis of CRP as a dichotomous variable based on the cut-off of 3mg/L

Logistic regression examining odds of having elevated hs-CRP also showed significantly positive associations between DII and HEI-2010 and hs-CRP (>3mg/L)

with DII showing 6% better predictive ability compared to HEI-2010 (DII_{Quartile 4vs1}, OR=1.37, 95% C.I. 1.12, 1.71, p-trend=0.001; HEI-2010_{Quartile 1vs4}, OR=1.31, 95% C.I. 1.12, 1.56, p-trend=0.002) (Table 2). Stratified results were similar to those observed with continuous CRP, the association between DII and dichotomous hs-CRP was slightly stronger than that of the HEI-2010 in the non-diabetic group (DII_{Quartile 4vs1}, OR=1.41, 95% C.I. 1.13, 1.76, p-trend=0.001; HEI-2010_{Quartile 1vs4}, OR=1.36, 95% C.I. 1.14, 1.63, p-trend=0.001), in the CVD group (DII_{Quartile 4vs1}, OR=1.67, 95% C.I. 1.04, 2.67, p-trend=0.05; HEI-2010_{Quartile 1vs4}, OR=1.52, 95% C.I. 0.97, 2.39, p-trend=0.04) and in the non CVD group (DII_{Quartile 4vs1}, OR=1.35, 95% C.I. 1.08, 1.69, p-trend=0.005; HEI-2010_{Quartile 1vs4}, OR=1.30, 95% C.I. 1.08, 1.58, p-trend=0.01) (Table 3). When stratified by race both DII and HEI-2010 showed significant positive association with hs-CRP (>3mg/l) in the non-Hispanic white group (DII_{Quartile 4vs1}, OR=1.51, 95% C.I. 1.17, 1.95, p-trend=0.001; HEI-2010_{Quartile 1vs4}, OR=1.40, 95% C.I. 1.15, 1.72, p-trend=0.001) (Table 4).

Discussion: The results from this study indicate that a diet high in pro-inflammatory food parameters such as cholesterol, saturated fat, and relatively poor in anti-inflammatory food parameters such as vegetables and fruits, is associated with increased inflammation as evidenced by increased levels of CRP with increasing DII scores. Overall, our study results are consistent with the hypothesis that diet modulates inflammation. The inference is that through this process of modulating inflammation, there will be an eventual effect on chronic diseases such as several cancers and cardiovascular diseases.

In our study positive association between DII and hs-CRP was observed only in the non-diabetic group, this could be due to healthier lifestyle adopted by participants who are diagnosed with diabetes which include consuming healthy diet, physical activity which can reduce inflammation. These subjects may also be on anti-diabetic medications like thiazolidinediones which apart from improving the hyperglycemic status also exert effect on molecular cascades and particularly some of those which regulate inflammatory process.(Buckingham 2005)

This is the first study in which DII has been compared to another dietary index. We observed slightly stronger associations with the DII compared to HEI-2010 for both CRP as continuous and as dichotomous outcome (6% better prediction of CRP >3mg/L for DII (quartile 4 vs 1) compared to HEI-2010 (quartile 1 vs 4). With its focus on the functional effects of foods, the DII is different from other dietary indices, virtually all of which fall into three main categories: 1. Those derived from specific dietary prescriptions based on some external standard [e.g., Healthy Eating Index (HEI) which was derived from the adherence to the US Dietary guidelines (Kennedy, Ohls et al. 1995)]; 2. Those derived empirically from findings within particular study populations [e.g., computing a pattern using principal component analysis (PCA)(Miller, Lazarus et al. 2010)] or 3. Those that link to particular cultural patterns of dietary intake (e.g., the Mediterranean diet score(Panagiotakos, Pitsavos et al. 2006)). The current study is different from the previous validation study(Shivappa 2013) in that NHANES is a nationally representative sample providing greater diversity in relation to race/ethnicity and regions of the US and socio-economic status.

Our study had several limitations that must be considered when interpreting these results. First, no cause-effect relations can be inferred from these cross-sectional data, and a single measure of diet notably reduces at least the precision (and, likely, the accuracy) of our estimates.. Residual confounding by imperfect measurement of covariates or failure to control for important, but unknown, confounders is always possible. In this study, DII has been compared to HEI-2010 which is only one of the many other indices available; future research may be warranted to compare the DII with other dietary indices.

In the DII validation study,(Shivappa 2013) sensitivity analysis was conducted with DII calculated from 27 food parameters whose data was derived from 7-day dietary records to predict CRP.(Shivappa 2013) In this current study, DII was calculated using just 26 food parameters from 24HR. Despite this, we still found significant positive associations between the DII and hs-CRP, demonstrating that that DII may be used in other studies where a smaller number of food parameters are available.

Conclusion: Results from this study indicate that both the DII and the HEI-2010 are associated with CRP, providing further evidence for a role of a healthy diet in mitigating chronic inflammation. Inflammation is a key biologic process in the development of cardiovascular diseases and certain cancers. Thus, the logical next step would be to examine the association between the DII and risk of chronic diseases.

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Table 4.1 Distribution of characteristics across quartiles of DII, NHANES Study 2005-2010

	Quartile 1 (n=3309)	Quartile2 (n=3306)	Quartile3 (n=3198)	Quartile4 (n=2998)	P-value ^{a,b}
Continuous variables, mean \pm standard deviation					
Age (years)	50.0 \pm 17.4	48.8 \pm 17.6	48.8 \pm 18.3	49.6 \pm 18.7	0.42
BMI (kg/m ²)	28.0 \pm 5.6	28.4 \pm 6.0	28.6 \pm 6.2	28.8 \pm 6.4	<0.0001
C-Reactive Protein (mg/L)	2.1 \pm 2.1	2.5 \pm 2.3	2.6 \pm 2.3	2.7 \pm 2.4	<0.0001
Categorical variables, n (percent)					
Sex					<0.0001
Males	1975 (59.7)	1809 (54.7)	1494 (46.7)	1093 (36.5)	
Females	1334 (40.3)	1497 (45.3)	1704 (53.3)	1905 (63.5)	
Education					<0.0001
Less than 9th Grade	342 (10.3)	382 (11.5)	403 (12.6)	453 (15.1)	
9-11th Grade (Includes 12th grade with no diploma)	402 (12.1)	488 (14.8)	552 (17.3)	584 (19.5)	
High School Grad/GED or Equivalent	660 (20.0)	773 (23.4)	766 (23.9)	807 (26.9)	
Some College or Associate Degree	887(26.8)	946 (28.6)	914 (28.6)	777 (25.9)	
College Graduate or Above	1017 (30.7)	716 (21.7)	561 (17.5)	376 (12.5)	
Race/Ethnicity					<0.0001
Mexican-American	654 (19.8)	653 (19.7)	575 (18.0)	505 (16.8)	
Other Hispanic	247 (7.5)	278 (8.4)	289 (9.0)	290 (9.7)	
Non-Hispanic White	1803 (54.5)	1634 (49.4)	1540 (48.2)	1397 (46.6)	
Non-Hispanic Black	433 (13.1)	572 (17.3)	651 (20.4)	692 (23.1)	
Other Race	172 (5.2)	169 (5.1)	143 (4.5)	114 (3.8)	
Insurance					0.01
Yes	2587(78.2)	2510 (75.9)	2406	2210 (73.7)	

			(75.2)		
No	721 (21.8)	795 (24.0)	791 (24.7)	785 (26.2)	
Diabetes					<0.0001
Yes	286 (8.6))	368 (11.1)	353 (11.0)	371 (12.4)	
No	2957 (89.4)	2884 (87.2)	2783 (87.0)	2571 (85.8)	
Hypertension					<0.0001
Yes	1023 (30.9)	997 (30.2)	1089 (34.0)	1066 (35.6)	
No	2280 (68.9)	2302 (69.6)	2105 (65.8)	1927 (64.3)	

^aContinuous variables were compared using ANOVA

^bCategorical variables were compared using Chi-square test

Table 4.2 Association between dietary indices and C-Reactive Protein, DII, NHANES Study 2005-2010

	Beta Estimate for log CRP ^a	95 % Confidence Interval	Odds Ratio for CRP > 3mg/L ^b	95 % Confidence Interval
Results for overall association between indices and CRP				
DII (Quartiles) ^c				
Quartile (2 vs 1)	0.15	0.10, 0.19	1.17	0.99, 1.38
Quartile (3 vs 1)	0.18	0.13, 0.23	1.30	1.10, 1.52
Quartile (4 vs 1)	0.19	0.13, 0.24	1.38	1.12, 1.68
P-trend	<0.0001		0.001	
HEI-2010 (Quartiles)				
Quartile (3 vs 4)	0.07	0.02, 0.12	1.09	0.93, 1.29
Quartile (2 vs 4)	0.13	0.08, 0.17	1.14	0.99, 1.31
Quartile (1 vs 4)	0.15	0.10, 0.20	1.32	1.12, 1.56
P-trend	<0.0001		0.002	

^a Beta estimates for log transformed CRP as outcome.

^b Outcome is CRP >3mg/L.

^c Models adjusted for age, energy, BMI, sex, race, physical activity, self reported hypertension, education, health insurance, physical activity, smoking history, diabetes, CVDs and marital status.

Table 4.3 Association between dietary indices and C-Reactive Protein after stratifying by diabetes and CVD, DII, NHANES Study 2005-2010

	Beta Estimate for log CRP ^a	95 % Confidence Interval	Odds Ratio for CRP > 3mg/L ^b	95 % Confidence Interval
Results stratified by diabetes status^d				
Diabetics (n=1430)				
DII (Quartiles)				
Quartile (2 vs 1)	0.05	-0.09, 0.19	1.33	0.82, 2.17
Quartile (3 vs 1)	-0.04	-0.19, 0.10	1.08	0.69, 1.71
Quartile (4 vs 1)	0.02	-0.14, 0.18	1.11	0.68, 1.82
P-trend	0.87		0.85	
HEI-2010 (Quartiles)				
Quartile (3 vs 4)	0.04	-0.08, 0.17	1.06	0.73, 1.60
Quartile (2 vs 4)	-0.31	-0.17, 0.11	0.86	0.60, 1.22
Quartile (1 vs 4)	0.02	-0.13, 0.17	1.08	0.72, 1.61
P-trend	0.98		0.96	
Non diabetics (n=12885)				
DII (Quartiles)				
Quartile (2 vs 1)	0.16	0.11, 0.20	1.15	0.97, 1.37
Quartile (3 vs 1)	0.20	0.15, 0.26	1.33	1.12, 1.58
Quartile (4 vs 1)	0.21	0.15, 0.27	1.41	1.13, 1.76
P-trend	<0.0001		0.001	
HEI-2010 (Quartiles)				
Quartile (3 vs 4)	0.07	0.02, 0.12	1.11	0.94, 1.32
Quartile (2 vs 4)	0.14	0.08, 0.19	1.18	1.02, 1.37
Quartile (1 vs 4)	0.17	0.11, 0.22	1.36	1.14, 1.63

P-trend	<0.0001		0.001	
Results stratified by CVD status^e				
CVD (n=1341)				
DII (Quartiles)				
Quartile (2 vs 1)	0.18	0.03, 0.34	1.52	1.01, 2.29
Quartile (3 vs 1)	0.21	0.06, 0.37	1.40	0.89, 2.21
Quartile (4 vs 1)	0.22	0.05, 0.39	1.67	1.04, 2.67
P-trend	0.007		0.05	
HEI-2010 (Quartiles)				
Quartile (3 vs 4)	-0.007	-0.14, 0.13	0.90	0.66, 2.39
Quartile (2 vs 4)	0.10	-0.05, 0.25	1.44	0.93, 2.25
Quartile (1 vs 4)	0.15	-0.003, 0.30	1.52	0.97, 2.39
P-trend	0.04		0.04	
Non CVD (n=11850)				
DII (Quartiles)				
Quartile (2 vs 1)	0.15	0.10, 0.20	1.15	0.97, 1.37
Quartile (3 vs 1)	0.18	0.13, 0.23	1.29	1.08, 1.54
Quartile (4 vs 1)	0.19	0.13, 0.25	1.35	1.08, 1.69
P-trend	<0.0001		0.005	
HEI-2010 (Quartiles)				
Quartile (3 vs 4)	0.08	0.03, 0.13	1.11	0.93, 1.32
Quartile (2 vs 4)	0.13	0.08, 0.17	1.11	0.96, 1.30
Quartile (1 vs 4)	0.15	0.10, 0.20	1.30	1.08, 1.58
P-trend	<0.0001		0.01	

^aBeta estimates for log transformed CRP as outcome.

^b Outcome is CRP >3mg/L.

^cFor analyses stratified by diabetes, models are adjusted for age, energy, BMI, sex, race, physical activity, self reported hypertension, education, health insurance, physical activity, smoking history, CVDs and marital status.

^dFor analyses stratified by CVD, models are adjusted for all variables in ^c plus diabetes and except CVD.

Table 4.4 Association between dietary indices and C-Reactive Protein after stratifying by race, DII, NHANES Study 2005-2010

	Beta Estimate	95 %	Odds Ratio for	95 %
Results stratified by race				
Mexican				
DII (Quartiles)				
Quartile (2 vs 1)	0.07	-0.03, 0.17	1.21	0.95, 1.54
Quartile (3 vs 1)	0.04	-0.07, 0.15	1.16	0.92, 1.46
Quartile (4 vs 1)	0.01	-0.12, 0.14	1.11	0.81, 1.53
P-trend	0.83		0.44	
HEI-2010				
Quartile (3 vs 4)	0.03	-0.07, 0.13	1.11	0.75, 1.64
Quartile (2 vs 4)	0.06	-0.04, 0.17	1.08	0.70, 1.67
Quartile (1 vs 4)	-0.02	-0.13, 0.10	1.31	0.94, 1.84
P-trend	0.97		0.17	
Other Hispanics				
DII (Quartiles)				
Quartile (2 vs 1)	0.15	-0.01, 0.31	0.90	0.56, 1.44
Quartile (3 vs 1)	0.27	0.09, 0.44	1.01	0.59, 1.74
Quartile (4 vs 1)	0.10	-0.08, 0.29	0.95	0.58, 1.56
P-trend	0.09		0.95	
HEI-2010				
Quartile (3 vs 4)	0.17	0.02, 0.33	1.17	0.69, 1.96
Quartile (2 vs 4)	0.10	-0.06, 0.26	0.81	0.51, 1.30
Quartile (1 vs 4)	0.07	-0.09, 0.24	0.99	0.56, 1.76
P-trend	0.49		0.68	
Non-Hispanic				
DII (Quartiles)				
Quartile (2 vs 1)	0.15	0.09, 0.22	1.18	0.97, 1.44
Quartile (3 vs 1)	0.19	0.12, 0.26	1.37	1.14, 1.65
Quartile (4 vs 1)	0.22	0.14, 0.30	1.51	1.17, 1.95
P-trend	<0.0001		0.001	
HEI-2010				
Quartile (3 vs 4)	0.08	0.01, 0.14	1.11	0.91, 1.36
Quartile (2 vs 4)	0.13	0.06, 0.20	1.17	1.00, 1.36
Quartile (1 vs 4)	0.19	0.12, 0.26	1.40	1.15, 1.72
P-trend	<0.0001		0.001	
Non- Hispanics				
DII (Quartiles)				
Quartile (2 vs 1)	0.02	-0.11, 0.15	0.98	0.69, 1.41
Quartile (3 vs 1)	0.04	-0.09, 0.17	1.06	0.78, 1.44
Quartile (4 vs 1)	-0.04	-0.18, 0.10	0.96	0.71, 1.30
P-trend	0.63		0.47	
HEI-2010				

Quartile (3 vs 4)	0.08	-0.05, 0.21	1.10	0.88, 1.39
Quartile (2 vs 4)	0.09	-0.03, 0.22	1.11	0.80, 1.53
Quartile (1 vs 4)	0.09	-0.04, 0.21	1.04	0.78, 1.38
P-trend	0.18		0.82	
Others (n=598)				
DII (Quartiles)				
Quartile (2 vs 1)	0.33	0.11, 0.55	1.78	0.76, 4.18
Quartile (3 vs 1)	0.38	0.13, 0.62	1.60	0.71, 3.60
Quartile (4 vs 1)	0.41	0.14, 0.62	2.05	0.97, 4.36
P-trend	0.001		0.06	
HEI-2010				
Quartile (3 vs 4)	-0.02	-0.23, 0.18	0.74	0.38, 1.45
Quartile (2 vs 4)	0.12	-0.11, 0.35	1.07	0.56, 2.07
Quartile (1 vs 4)	0.12	-0.13, 0.37	1.21	0.68, 2.15
P-trend	0.24		0.44	

^aBeta estimates for log transformed CRP as outcome.

^b Outcome is CRP >3mg/L.

^cFor analyses stratified by race, models are adjusted for age, energy, BMI, sex, race, physical activity, self reported hypertension, education, health insurance, physical activity, smoking history, diabetes, CVD and marital status

CHAPTER 5

Dietary Inflammatory Index (DII) and mortality in NHANES III Study.

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ABSTRACT

Background: Various dietary components have been studied in relation to overall mortality; however, little is known about the relationship between the inflammatory potential of overall diet and mortality. **Materials and Methods:** We examined the association between the dietary inflammatory index (DII) and mortality in the National Health and Nutrition Examination Survey (NHANES) III follow-up study. The DII was computed from baseline dietary intake assessed using 24-h dietary recalls (1988-94). Mortality was determined from the National Death Index records through 2006. Cox proportional hazards regression was used to estimate hazard ratios. During the follow-up period through the end of 2006, 2795 deaths were identified, including 615 due to cancer, 158 of which were due to digestive-tract cancer, and 1233 due to cardiovascular disease (CVD). **Results:** Multivariable analysis, adjusting for race, diabetes status, hypertension, physical activity, BMI, poverty index and smoking, revealed positive associations between higher DII and mortality. Comparing subjects in DII Tertile 3 vs Tertile 1, significant associations were noted for all-cause mortality ($HR_{\text{Tertile3vs1}}=1.34$; 95%CI 1.19-1.51, $P_{\text{trend}}<0.0001$), cancer-related mortality ($HR_{\text{Tertile3vs1}}=1.46$; 95%CI 1.10-1.96, $P_{\text{trend}}=0.01$), digestive-tract cancer mortality ($HR_{\text{Tertile3vs1}}=2.10$; 95%CI 1.15- 3.84, $P_{\text{trend}}=0.03$) and CVD mortality ($HR_{\text{Tertile3vs1}}=1.46$; 95%CI 1.18-1.81, $P_{\text{trend}}=0.0006$). **Conclusion:** These results indicate that a pro-inflammatory diet, as indicated by higher DII scores, was associated with overall, all-cancer, digestive tract cancer, and CVD mortality.

Introduction: Inflammation is a result of the body's response to tissue insult or injury, or the presence of inflammatory stimulants.(Keibel, Singh et al. 2009; Pan, Lai et al. 2009) The acute inflammatory response represents an important step in the process of

wound healing and tissue regeneration that, under normal circumstances, will lead to recovery within a few days. (Thun, Henley et al. 2004; Warnberg, Gomez-Martinez et al. 2009) Chronic inflammation is known to be associated with common epithelial cancers, with colorectal (Chung and Chang 2003; Terzic, Grivennikov et al. 2010; Toriola, Cheng et al. 2013) being the most intensively studied. Worldwide, CVD is the leading cause of mortality, accounting for about half of the deaths among adults.(2008) In the United States, more than 80 million people suffer from CVD, and an average of about one million Americans die from CVD each year. (Calabro, Golia et al. 2009; Lloyd-Jones, Adams et al. 2009) There is growing evidence that specific dietary components influence inflammation (de Mello, Schwab et al. 2011; Khoo, Piantadosi et al. 2011; Luciano, Mottus et al. 2012) and all-cause, cancer and cardiovascular disease (CVDs) mortality.(Cohen, Hailpern et al. 2008; Deng, Song et al. 2013; Chang, Lazo et al. 2014; Cheung, Sahni et al. 2014)

Research into the role of diet in inflammation and mortality suggests that diet represents a complicated set of exposures which often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes. Several dietary indices exist to assess diet quality, but none had focused on diet's effects on inflammation until researchers at the University of South Carolina's Cancer Prevention and Control Program developed the Dietary Inflammatory Index (DII), which can be used in diverse populations to assess the inflammatory potential of diet assessed by various dietary assessment tools [e.g., 24-hour dietary recalls (24HR), food frequency questionnaires (FFQs) and food records]. (Shivappa 2013; Wood 2014) To date, validation of the DII has shown its ability to predict serum CRP levels in a large longitudinal epidemiological

study.(Shivappa 2013) Previously, we observed that shift workers tend to have a pro-inflammatory diet (higher DII scores) compared to their day working counterparts.(Wirth, Burch et al. 2014) Furthermore, higher DII scores have been linked to asthma.(Wood 2014)

However, the DII has not yet been applied to a population with mortality outcomes. The purpose of this study is to examine the association between the DII and all-cause, overall cancer, digestive-tract cancer, and CVD mortality in a large prospective cohort of a nationally representative study, the National Health and Nutrition Examination Survey (NHANES III). Our working hypothesis is that a higher DII score (indicating a pro-inflammatory diet) increases risk of dying from any cause and also dying from specific causes (overall and digestive-tract cancers and CVDs).

Methods:

Subjects providing data for this analysis were participants in the NHANES III (1988–1994), which is a nationally representative sample of the civilian, noninstitutionalized US population. Details of the survey design have been reported previously.(1994) The current study was restricted to participants above 19 years of age at baseline, with complete data on mortality status, diet, and relevant covariates (n = 12,366).

In the NHANES III cohort study, mortality information is derived on the basis of a probabilistic match between NHANES III and the National Death Index records through 31 December 2006 by the National Center for Health Statistics. For overall mortality we included deaths from all causes. For cancer-specific mortality we included deaths from malignant neoplasms which were coded from C00-C97 in the International

Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10).

For digestive-tract cancers we included malignant neoplasms from the front of the mouth to the rectum and malignant neoplasms of pancreas and hepato-biliary system (ICD-10=C00-C16, C18-C22, C25). For CVD related mortality we used ICD-10=I00-I178.

Dietary information was obtained from an in-person 24HR with the use of a personal computer-based, automated, interactive data collection and coding system that was developed by the University of Minnesota's Nutrition Coordinating Center, and conducted by trained interviewers. 24HR-derived dietary data were used to calculate DII scores for all participants. The DII is based on literature published through 2010 linking diet to inflammation. Developing the DII involved review and scoring nearly 2000 scientific articles on cell culture and laboratory animal experiments, and cross-sectional, longitudinal and intervention trials in humans of diet and six inflammatory markers [i.e., CRP, interleukin (IL)-1 β , IL-4, IL-6, IL-10, and tumor necrosis factor (TNF)- α]. Individual intakes of food parameters on which the DII is based are then compared to a world standard database of dietary intake based on datasets from 11 different regions worldwide. A complete description of the DII is available elsewhere.(Cavichia, Steck et al. 2009; Shivappa 2013) Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the world database that provided a robust estimate of a mean and standard deviation for each parameter.(Shivappa 2013) These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of

“right skewing,” this value is then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed to create the overall DII score for every participant in the study.(Shivappa 2013)A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, also is available.(Shivappa 2013)

Associations with DII for demographic factors, lifestyle factors, self-reported diabetes mellitus, anthropometric characteristics, and weights and servings of food groups were examined using ANOVA models or χ^2 tests (see Table 1 for specific variables). DII was analyzed both as a continuous variable and by tertiles of exposure in relation to various mortality outcome variables, consisting of all-cause, overall cancer, digestive-tract cancer and CVD-related mortalities. Hazard ratios and 95% confidence intervals (HR; 95% CI) were estimated using Cox proportional hazards regression models, adjusting only for age in the first model and additionally adjusting for body mass index [BMI = weight (kg)/weight (m)²], smoking status, sex, race, diabetes status, hypertension status, physical activity, and poverty index (PI) in the second model. Physical activity was assessed by questionnaire and coded as the number of moderate to vigorous intensity activities in the past month; PI was used to capture socioeconomic status, the poverty to income ratio is an index of poverty status which is calculated by dividing family income by a poverty threshold specific to family size. The covariates

were chosen *a priori* as they were shown previously to be strong risk factors for the outcomes of interest in this cohort. Participants with extreme energy intake values (≤ 500 kcals and ≥ 5000 kcals), with abnormal BMI values ($> 50 \text{ kg/m}^2$) or PI values (> 10), or who had a history of cancer at baseline were excluded. Energy was not included in the model because energy is a component of the DII. A linear test for trend was conducted by including the median value for each DII tertile as a continuous term into the regression model. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated. Statistical tests were performed using SAS[®] 9.3, (SAS Institute Inc., Cary, NC); all statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Results:

DII had a mean \pm SD value of 0.73 ± 2.20 . BMI, C-Reactive Protein (CRP) and age increased across tertiles of DII. Intake of the following dietary variables decreased across DII tertiles (Table 1): total gram weight of food and beverages, energy, dietary fiber, total grains, total fruits, vegetables, and meat. Individuals in tertile 3 had higher percentage of females, non-Hispanic Blacks, people with low PI and hypertension (Table 2). There was a higher percentage of deaths observed in tertile 3 compared to tertile 1 for all-cause mortality (35.9% vs 30.4%), overall cancer mortality (38.1% vs 31.1%), digestive-tract cancer mortality (42.4% vs 29.1%) and CVD mortality (35.4% vs 29.8%) (Table 2). During the follow-up period (mean \pm SD = 13.5 ± 4.0 years), 2801 total deaths were identified, including 617 malignant cancer deaths, 158 digestive-tract cancer deaths, and 1235 CVD deaths. No significant interactions were observed between DII and either

sex or BMI. When analyses were carried out using continuous DII, a 1-unit increment in DII (corresponding to 0.5 standard deviation increase) showed significant positive associations with risk of overall mortality after adjusting for age (HR=1.05; 95%CI 1.02 - 1.08). After additional adjustment for sex, race, diabetes status, hypertension, physical activity, BMI, PI and smoking, the HR was slightly attenuated (1.04; 95%CI 1.02 - 1.07). For analysis focusing on deaths due to specific causes, a significant positive association was observed with CVD mortality after adjustment for covariates (HR=1.06; 95%CI 1.02 - 1.09). For malignant cancer mortality and digestive-tract cancer mortality, HRs for DII were in the hypothesized direction as was observed for all-cause and CVD mortality; however, results did not achieve statistical significance, consistent with the smaller number of cases (Table 3).

Analysis with DII categorized as tertiles revealed significantly higher risk for subjects in the third tertile compared to those in the first tertile for overall mortality (HR=1.34; 95%CI 1.19 - 1.51, $P_{\text{trend}} < 0.0001$); for malignant cancer mortality (HR=1.46; 95%CI 1.10 - 1.96, $P_{\text{trend}} = 0.01$); digestive cancer mortality (HR=2.10; 95%CI 1.15 - 3.84, $P_{\text{trend}} = 0.03$) and CVD mortality (HR=1.46; 95%CI 1.18 - 1.81, $P_{\text{trend}} = 0.0006$) (Table 3).

Discussion:

In this large, nationally representative, prospective cohort study, the consumption of a more pro-inflammatory diet, as reflected by higher DII scores, was associated with increased risk of deaths from any cause, deaths due to malignant cancer, deaths due to digestive-tract cancer, and deaths due to cardiovascular diseases. Compared to subjects in tertile 1, those in tertile 3 were 34% more likely to die from any cause, 46% more likely to die from malignant cancers, 110% more likely to die from digestive-tract cancers and

46% more likely to die from cardiovascular diseases. We also observed a significantly increasing trend of CRP across tertiles of DII. These results are consistent with the epidemiology of colorectal cancer, which is known to be strongly related to inflammation (Erlinger, Platz et al. 2004; Nikiteas, Tzanakis et al. 2005; Gunter, Stolzenberg-Solomon et al. 2006; Otani, Iwasaki et al. 2006) and represents the majority of digestive-tract cancers.

The DII is different from other dietary indices, virtually all of which fall into three main categories: 1. Those derived from specific dietary prescriptions based on some external standard [e.g., Healthy Eating Index (HEI) which was derived from the adherence to the US Dietary guidelines (Kennedy, Ohls et al. 1995)]; 2. Those derived empirically from findings within particular study populations [e.g., computing a pattern using principal component analysis (PCA)(Miller, Lazarus et al. 2010)] or 3. Those that link to particular cultural patterns of dietary intake (e.g., the Mediterranean diet score (Panagiotakos, Pitsavos et al. 2006)). Studies have been conducted to examine various dietary patterns and indices in relation to mortality.(Mitrou, Kipnis et al. 2007; Akbaraly, Ferrie et al. 2011; Rathod, Bharadwaj et al. 2012) In a study conducted in the NHANES III cohort study, HEI was found to be inversely associated with overall and CVD mortality.(Rathod, Bharadwaj et al. 2012) In a study conducted in the NIH-American Association of Retired Professionals (NIH-AARP) cohort, the Mediterranean diet score was associated with reduced all-cause and cause-specific mortality,(Mitrou, Kipnis et al. 2007) while another report from the NIH-AARP study showed various indices [HEI-2010, the Alternative Healthy Eating Index-2010 (AHEI-2010), the alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH)] to

be protective against all-cause mortality, CVD and cancer mortality.(Reedy, Krebs-Smith et al. 2014) In contrast, in the Whitehall cohort study, which was conducted in United Kingdom with a predominantly Caucasian population AHEI was not associated with cancer mortality or non-cancer/non-CVD mortality.(Akbaraly, Ferrie et al. 2011)

Previous studies also have examined the effect of specific food items, such as red meat,(Pan, Sun et al. 2012; McCullough, Gapstur et al. 2013; Takata, Shu et al. 2013; Larsson and Orsini 2014) and nutrients, such as calcium,(Li, Kaaks et al. 2011) magnesium(Li, Kaaks et al. 2011) and vitamin E,(Pocobelli, Peters et al. 2009) on mortality. No association was observed between magnesium and calcium and cancer-related mortality in the EPIC-Heidelberg study.(Li, Kaaks et al. 2011) In a prospective study conducted by Pocobelli et al., vitamin E was found to significantly reduce CVD mortality; however, no association was observed with cancer mortality. (Pocobelli, Peters et al. 2009) A limitation of that approach is that these whole foods or nutrients are usually consumed with other food items and nutrients; thus, dietary intercorrelations may attenuate or accentuate the actual effects of the whole food or nutrient under study. A very high correlation between nutrients among foods can result in instability in risk estimation and possible loss of statistical power. In formulating the DII,(Cavicchia, Steck et al. 2009; Shivappa 2013) an entirely different approach was taken by focusing on the functional effects of foods and nutrients. As such, it relies on the very careful review and scoring of the medical literature in specific relation to inflammation. Also, it standardizes individuals' dietary intakes of pro- and anti-inflammatory food constituents to world referent values.

Although the actual mechanism of how the healthy diet reduces mortality is not clearly known, one of the possible mechanisms for this inverse association might be through the effect of pro-inflammatory diet on insulin resistance by increasing systemic inflammation.(Festa, D'Agostino et al. 2000; Esmailzadeh, Kimiagar et al. 2007)

Consumption of food items such as meat and butter have been shown to increase systemic inflammation by increasing levels of high-sensitivity CRP, E-selectin and soluble vascular cell adhesion molecule-1,(Esmailzadeh, Kimiagar et al. 2007) which then are responsible for increasing insulin resistance.(Festa, D'Agostino et al. 2000)

Insulin resistance caused by increasing circulating levels of insulin, triglycerides, and non-esterified fatty acids, (Bruce, Giacca et al. 2000; Bruce, Wolever et al. 2000) is associated with digestive-tract cancers and various cardiovascular diseases all of which, if left uncontrolled, result in death. As mentioned previously, there are various dietary factors that have different effects on inflammation; for example, red meat consumption increases inflammation and green leafy vegetables reduce inflammation.(Bruce, Giacca et al. 2000; Bruce, Wolever et al. 2000) Supporting our findings, previous work in the NHANES III examining diet and mortality has shown significant inverse associations between anti-inflammatory food parameters such as selenium,(Eaton, Abdul Baki et al. 2010) magnesium,(Deng, Song et al. 2013) and vitamin K(Cheung, Sahni et al. 2014) intake and mortality. A significant positive association was observed between sodium intake and sugar intake and CVD mortality.(Cohen, Hailpern et al. 2008; Yang, Zhang et al. 2014) No association was observed between meat intake and mortality.(Kappeler, Eichholzer et al. 2013)

Our study has several strengths. NHANES III Study is a large, prospective, multiethnic, nationally representative study well-characterized with data on multiple risk factors and confounders. This study had a long follow-up with a large number of events for the outcomes studied. Nevertheless, there are limitations. The main limitation of this study was that the estimation of dietary intake was based on single self-reported 24HR, which may not reflect the regular dietary habit of individuals, and hence can lead to potential misclassification bias. Dietary assessment was available only at one time point. Participants' dietary habit might have changed during the follow-up period. However, previous studies reported that dietary pattern classification is moderately stable over time.(Jensen, Wahrendorf et al. 1984; Jain, Howe et al. 1989; Lindsted and Kuzma 1989; Thompson, Metzner et al. 1990; Sijtsma, Meyer et al. 2012; Mursu, Steffen et al. 2013)

In conclusion, individuals who consumed a more pro-inflammatory diet were at increased risk of dying from any cause, from all malignancies, from digestive-tract cancers, and from CVD compared to individuals who consumed a more anti-inflammatory diet. Our results provide further evidence for the benefits of a diet high in vegetables and fruits, nuts, low-fat dairy products, fish, and whole grains and low in fried foods, processed meats and refined grains¹. Future steps might include investigating how the DII behaves longitudinally in an intervention trial among individuals who have had cancer or CVD to examine if improvement in the DII scores over time is associated with subsequent symptom improvement. It also would be interesting to examine how DII fares in predicting mortality in studies outside United States reflecting different racial makeup,

and how it compares with other indices in relation to overall mortality and cause-specific mortality.

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Table 5.1 Distribution of continuous baseline characteristics of NHANES III cohort across tertiles of DII

Characteristics ^a	Tertile 1 (N=4183)	Tertile 2 (N=4136)	Tertile 3 (4119)	P-value ^a
Age(yrs)	47.06±18.9	47.05±19.1	48.10±19.3	0.009
BMI (kg/m ²)	26.51±4.9	26.7±5.2	26.9±5.4	0.0001
C-Reactive Protein (mg/l)	2.94±1.8	3.11±1.9	3.21±2.1	<0.0001
Total grams of food and beverages consumed	2973 ±1235.4	2241±985.0	1663±782.8	<0.001
Grains (serv/week)	8.75 ±5.0	6.38±3.4	4.80±2.7	<0.0001
Fruits	2.42±2.87	1.41±1.86	0.78±1.25	<0.0001
Vegetables	4.82±3.17	2.78±2.0	1.53±1.40	<0.0001
Meat	2.9±2.1	2.3±1.6	1.5±1.1	<0.0001

^aContinuous variables examined using ANOVA presented as mean±s.d.

Table 5.2 Distribution of categorical baseline characteristics of NHANES III cohort across tertiles of DII

Characteristics ^a	Tertile 1 (N=4183)	Tertile 2 (N=4136)	Tertile 3 (4119)	P-value ^a
Sex				<0.0001
Males	2638 (43.7)	1958 (32.4)	1439 (23.8)	
Females	1545 (24.1)	2178 (34.0)	2680 (41.9)	
Income status based on poverty index^{b,c}				<0.0001
Low	1091 (27.9)	1297 (33.2)	1521 (38.9)	
Middle	1871 (33.5)	1872 (33.5)	1841 (33.0)	
High	1221 (41.5)	967 (32.8)	757 (25.7)	
Race/Ethnicity				<0.0001
Non-Hispanic White	1998 (37.3)	1770 (33.0)	1591 (29.7)	
Non-Hispanic Black	839 (25.9)	1076 (33.1)	1330 (41.0)	
Mexican-American	1181 (35.3)	1119 (33.5)	1041 (31.2)	
Others	165 (33.5)	171(34.5)	157 (31.9)	
Hypertension	1033 (32.3)	1043 (32.7)	1118 (35.0)	0.03
Diabetes	1798 (32.5)	1859 (33.6)	1869 (33.8)	0.44
Mortality status				<0.0001
Total Deaths	852 (30.4)	944 (33.7)	1005 (35.9)	
Cancer deaths	192 (31.1)	190 (30.8)	235 (38.1)	0.02
Digestive-tract cancer deaths	46 (29.1)	45 (28.5)	67 (42.4)	0.04
CVD deaths	368 (29.8)	430 (34.8)	437 (35.4)	0.004

^aCategorical variables examined using Chi-square test presented as n (%).

^b Poverty Index (PI) is a calculated variable based on family income and family size using tables published each year by the Bureau of the Census in a series “Current Population reports” on poverty in the United States.

^c Low income status= $0.000 \leq PI \leq 1.300$, Middle Income status = $1.301 \leq PI \leq 3.500$,High Income status= $PI > 3.500$.

Table 5.3 Hazards ratio for mortality outcomes with DII as continuous and as tertiles

	Overall Mortality (N=2795)		Cancer Mortality (N=615)		Digestive-tract cancer mortality ^c (N=158)		Cardiovascular disease mortality (N=1233)	
	HR ^a (95%CI)	HR ^b (95%CI)	HR ^a (95%CI)	HR ^b (95%CI)	HR ^a (95%CI)	HR ^b (95%CI)	HR ^a (95%CI)	HR ^b (95%CI)
DII (continuous)	1.05 (1.02, 1.08)	1.04 (1.02, 1.07)	1.05 (0.98, 1.12)	1.04 (0.97,1.11)	1.09 (0.95, 1.25)	1.08 (0.95, 1.22)	1.05(1.02, 1.09)	1.06 (1.02, 1.09)
Tertile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertile 2	1.24 (1.10, 1.40)	1.23 (1.10, 1.37)	1.32 (1.004, 1.74)	1.30 (0.99, 1.70)	1.29 (0.72, 2.31)	1.31 (0.76, 2.26)	1.26 (1.08, 1.49)	1.28 (1.09, 1.50)
Tertile 3	1.37 (1.20, 1.56)	1.34 (1.19, 1.51)	1.49 (1.12, 2.00)	1.46 (1.10, 1.96)	2.14 (1.13, 4.05)	2.10 (1.15, 3.84)	1.43 (1.16, 1.77)	1.46 (1.18, 1.81)
p-trend	<0.0001	<0.0001	0.007	0.01	0.03	0.03	0.0008	0.0006

^a Age-adjusted

^b Additionally adjusted for sex, race, diabetes status, hypertension, physical activity, BMI, poverty index and smoking

^cIncludes cancers from beginning of oral cavity to rectum and cancers of pancreas and hepato-biliary system.

CHAPTER 6

Association between dietary inflammatory index and metabolic and inflammatory markers in a dietary intervention trial

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ABSTRACT

Background: Various components of diet can modulate inflammation and metabolic factors. However, little is known about how the inflammatory potential of diet can affect inflammatory and metabolic markers. **Objective:** this study we examine the associations between a novel evidence-based dietary inflammatory index (DII) and inflammation and metabolic factors in an intervention study. **Method:** Data were obtained from 240 individuals with MetSyn (MetSyn) randomized to one of two interventions: 1) a high-fiber diet and 2) the American Heart Association (AHA) diet. DII was calculated using 24-h dietary recalls at baseline, 6-month follow-up, and 12-month follow-up, and was analyzed with metabolic markers [insulin, blood glucose and homeostasis model assessment (HOMA-IR)] and inflammatory markers [C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)], as outcomes using linear mixed models adjusted for covariates. All biomarkers were log transformed to meet model assumptions. **Results:** At all follow-up time points, DII was lower in the high-fiber group compared to the AHA group. Compared to DII tertile 1 participants, those in tertile 3 (reflecting a more pro-inflammatory diet) had higher insulin (β : 0.15; 95% CI: 0.01, 0.28), glucose (β : 0.03; 95% CI 0.01, 0.05), HOMA-IR (β : 0.18; 95% CI 0.03, 0.32) and IL-6 values (β : 0.13; 95% CI 0.02, 0.25). No significant associations were observed with CRP and TNF- α . **Conclusion:** Results demonstrated that a successful dietary intervention can produce changes in DII scores that, in turn, predict changes in insulin, fasting glucose, HOMA-IR and IL-6. These findings provide further evidence that consuming a more anti-inflammatory diet is associated with reductions in markers of

insulin resistance and inflammation and that the DII can be used as a tool to link diet-induced inflammation to levels of metabolic and inflammatory biomarkers.

Introduction: The MetSyn (MetSynyn) consists of a cluster of several metabolic and physiological abnormalities, including obesity, impaired glucose regulation, dyslipidemia and hypertension. Owing to its association with the increased risk of developing type 2 diabetes and cardiovascular disease (CVD)(Ford 2005), MetSynyn has become the subject of considerable interest in both research and clinical practice. Lifestyle modifications are foremost in the treatment of MetSyn. Therefore, treating or preventing the progression of this disease through modifiable life-style factors, such as dietary behaviors, is crucial. While several theories have been proposed in the etiology and progression of MetSyn, they all tend to point to inflammation as a key factor in the pathogenesis of the disease(Grundy 2003).

Inflammation is a response due to repeated “injury;” e.g. from cigarette smoking, infection or hypertension, and evidence is accumulating on the role of chronic inflammation in chronic diseases such as diabetes(van Beek, Lips et al. 2014) and MetSyn.(Grundy 2003) Dietary factors also have been associated with inflammation and metabolic risk factors. The Western-type diet, which is high in red meat, high-fat dairy products, and refined grains, has been associated with higher levels of CRP, IL-6 and fibrinogen.(King, Egan et al. 2003; Johansson-Persson, Ulmius et al. 2013) On the other hand, the Mediterranean diet, which is high in whole-grains, fruit and green vegetables and fish, low in red meat and butter, with moderate alcohol and olive oil intake, has been associated with lower levels of inflammation.(Estruch, Martinez-Gonzalez et al. 2006) Dietary factors also affect markers of insulin resistance, such as homeostasis model

assessment (HOMA-IR). In a cross-sectional study conducted in Japan, coffee consumption was shown to be inversely associated with HOMA-IR and in the same study green tea consumption was positively associated with HOMA-IR.(Pham, Nanri et al. 2014) Administration of flaxseed in an intervention trial was shown to reduce levels of insulin and glucose in overweight or obese individuals with pre-diabetes.(Hutchins, Brown et al. 2013)

The dietary inflammatory index (DII) was developed to provide an overall score for the inflammatory potential of the diet.(Cavicchia, Steck et al. 2009; Shivappa, Steck et al. 2013) The DII is based upon an extensive literature search incorporating cell culture, laboratory animal, and epidemiologic studies on the effect of diet on inflammation. The overall score is dependent on the whole diet, not just certain nutrients or foods. DII scoring is not dependent on population means or recommendations of intake; it is based on results published in the scientific literature (a total of 1943 articles were scored). The DII is not limited to micronutrients and macronutrients, but also incorporates commonly consumed components of the diet including flavonoids, spices, and tea. Thus far, construct validation of the DII has shown its association with serum CRP levels in a large longitudinal epidemiological study.(Shivappa, Steck et al. 2013) Previously, we observed that shift workers tend to have a pro-inflammatory diet (higher DII scores) compared to their day-working counterparts.(Wirth, Burch et al. 2014) Furthermore, higher DII scores have been linked to asthma.(Wood, Shivappa et al. 2014) A modification of the older version of this index has been shown to be associated with inflammatory markers, HOMA-IR and fasting glucose levels in a couple of studies in the

Netherlands.(van Woudenberg, Theofylaktopoulou et al. 2013; Hebert, Shivappa et al. 2014)

In this study, we test the hypothesis that participants with higher DII scores, indicating a more pro-inflammatory diet, will have elevated levels of metabolic inflammatory markers. compared to those consuming a more anti-inflammatory diet.

Methods:

Briefly, the CAN DO study is a dietary intervention trial conducted at the University of Massachusetts Medical School (UMMS), Worcester, Massachusetts, USA from May 2009 to February 2013. The study protocol was approved by the UMMS Institutional Review Board for use of human subjects in medical research and all participants gave informed consent. To be included in the study individuals had to meet at least three of the components of MetSynyn, be non diabetic, have a body mass index (BMI) $>30 \text{ mg/kg}^2$ but $<40 \text{ mg/kg}^2$, and have a fasting blood sugar $\leq 126 \text{ mg/dl}$. In total 240 participants were recruited, deemed to be eligible, and randomized into one of the two dietary interventions: a high-fiber diet or the American Heart Association (AHA) diet. In the high-fiber diet condition, participants received instruction to achieve a daily dietary goal of $\geq 30\text{g}$ fiber intake from a variety of food sources. Participants in AHA diet group were instructed to make dietary changes addressing both macro- and micronutrients as recommended by the AHA 2006 dietary guidelines. There was no control arm in this study.

Data were obtained at baseline on demographic characteristics including age; race/ethnicity, education, marital status, household income, and employment status using a self-administered questionnaire. Anthropometric data and blood were collected at

baseline, 6-month and 12-month visits. BMI [weight(kg)/height(m)²] was calculated for each time point and was categorized as mild [class I, BMI 30 to <35] or moderate (class II, BMI 35 to 40) obesity. Serum was collected after a 12-h fast and stored at -80°C. To measure insulin, IMMUNLITE 2000 insulin was used, it is a solid-phase, enzyme-labeled chemiluminescent immunometric assay. The SYNCHRON LX System was used to measure glucose; it determines GLUCm concentration by an oxygen rate method employing a Beckman Coulter oxygen electrode. Insulin resistance, assessed by the homeostasis model assessment (HOMA-IR), was calculated as follows: $\text{HOMA-IR} = \text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mg/dL)} / 405$. (Matthews, Hosker et al. 1985) Basic clinical data assessment and routine biochemical assays were performed as described previously. (Rietzschel, De Buyzere et al. 2007) In addition, levels of three inflammatory markers were measured: high-sensitive C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).

Dietary Intake (Hoebeeck, Rietzschel et al. 2011) and Dietary Inflammatory Index (DII) (Cavichia, Steck et al. 2009; Shivappa 2013)

Diet was assessed through three 24-h dietary recalls (24HR) administered by trained registered dietitians at baseline, 3-, 6- and 12-month visits using the Nutritional Data System for Research (NDS-R) software. (Nutrition Coordinating Center) The participants received a food portion visual booklet prior to receiving the assessment calls to facilitate portion size estimation. This 24HR- derived dietary information was used to calculate DII scores for all subjects, as described in detail elsewhere. (Cavichia, Steck et al. 2009; Shivappa, Steck et al. 2013) Briefly to describe the methods involved in DII calculation, the dietary data for each study participant were first linked to the regionally

representative global database that provided a robust estimate of a mean and standard deviation for each of the food parameters (i.e., foods, nutrients, and other food components such as flavonoids) considered,(Shivappa, Steck et al. 2013) to derive a z-score, by subtracting the “standard global mean” from the amount reported and dividing this value by the standard deviation. To minimize the effect of “right skewing” (a common occurrence with dietary data), this value was then converted to a centered percentile score which was then multiplied by the respective food parameter effect score (derived from a literature review and scoring of 1943 articles) to obtain subject’s food parameter-specific DII score. All of the food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. Data were available from 29 food parameters.

Statistical analysis:

Means and standard deviations of DII were calculated at each time point for both of the intervention groups, and the trend in DII across the time points were plotted using line graphs. Insulin, blood glucose, HOMA-IR, hs-CRP, IL-6 and TNF- α were log transformed as they were not normally distributed. DII was analyzed as both continuous and grouped into tertiles.

All statistical analyses were carried using SAS[®] statistical software package version 9.3 (SAS Institute Inc., Cary, NC). Comparisons of baseline characteristics across tertiles of DII were made using χ^2 tests for categorical variables and ANOVA for continuous variables. . Multivariable analyses were carried out with log transformed metabolic (insulin, glucose and HOMA-IR) and inflammatory biomarkers (CRP, IL-6

and TNF- α) as outcomes.. Sex, race/ethnicity, time-points, high triglycerides, BMI, and intervention group were considered as covariates due to their potential associations with insulin resistance. Linear mixed models with random intercepts were used. All analyses were performed using SAS[®] version 9.3 software.

Results:

Figure 1 displays the distribution of mean DII across time points in both intervention groups. DII decreases to a greater extent in the fiber group than in the AHA group. Although mean DII at baseline in the fiber group was higher than that in the AHA group, at 12 months the mean DII in fiber group was lower than that in the AHA group (fiber vs AHA= -0.29 vs 0.10, p-value=0.10), the decreases of DII in the fiber group was 0.54 unit, while the decrease was 0.21 unit in the AHA group (p-value=0.25) .

Table 1 shows the baseline characteristics of the participants across tertiles of DII. For continuous variables, total fiber intake, total energy intake, and physical activity have a significant decreasing trend, whereas IL-6 and TNF- α have a significant increasing trend across tertiles of DII. For continuous variables, means of triglycerides and HDL-C tended to decrease and means of diastolic blood pressure, hs-CRP, fasting plasma glucose and fasting plasma insulin levels tended to increase across tertile of DII in this study sample, but there was not enough evidence to detect a trend in the population. For categorical variables, individuals in tertile 3 were more likely to be females and were more likely to have BMI ≥ 35 kg/m² compared to individuals in tertile 1.

Metabolic biomarkers: DII as a continuous independent variable was associated with insulin (β : 0.03; 95% CI: 0.00, 0.06), glucose (β : 0.01; 95% CI: 0.00, 0.01) and

HOMA-IR (β : 0.11; 95% CI: 0.02, 0.21), When DII was analyzed as tertiles, individuals in tertile 3 (reflecting a more pro-inflammatory diet) had higher insulin (β : 0.15; 95% CI: 0.01, 0.28), glucose (β : 0.03; 95% CI 0.01, 0.05) and HOMA-IR (β : 0.18; 95% CI 0.03, 0.32), (Table 2.)

Inflammatory biomarkers: Continuous DII was associated with IL-6 (β : 0.03; 95% CI: 0.01, 0.05). When DII was analyzed as tertiles, individuals in tertile 3 (reflecting a more pro-inflammatory diet) had higher IL-6 (β : 0.13; 95% CI: 0.02, 0.25), No significant association was observed for hs-CRP or TNF- α , although the direction of association suggested a positive association with DII. (Table 3).

Discussion:

The results from this study demonstrated that a diet focused on increasing dietary fiber result in greater decrease in DII than the AHA diet, dietary fiber produces lower level of inflammation and insulin resistance as evident from the lower values of DII for the ‘fiber’ group compared to ‘AHA’ group. Although this is consistent with the finding from previous research showing fiber to be strongly protective against chronic inflammation,(Buyken, Goletzke et al. 2014) it is the first study demonstrated that DII can be manipulated in a dietary trial. Dietary fiber has been previously demonstrated to be a useful component of weight loss and weight loss maintenance(Howarth, Saltzman et al. 2001; Lairon 2007) and it acts directly on several aspects of the MetSyn including maintaining glucose and lipid homeostasis, and improving hypertension and insulin control.(Galisteo, Duarte et al. 2008; Weickert and Pfeiffer 2008)

Fiber also forms an important component of DII with a very negative inflammatory effect score of -0.663.(Shivappa, Steck et al. 2013) We also observed a strong positive association between DII and metabolic markers, including insulin, glucose and HOMA-IR. This is consistent with the previous finding from this study which examined the association between dietary magnesium and metabolic factors.(Wang, Persuitte et al. 2013) Magnesium also forms a component of DII with negative inflammatory effect score of -0.484.(Shivappa, Steck et al. 2013) We found an independent positive association between consuming a more pro-inflammatory diet (increasing DII score) and plasma levels of IL-6, but not CRP and TNF- α . This could be due to the observations from previous studies which have shown that IL-6 is a more sensitive indicator of atherosclerosis and cardiovascular risk than CRP and TNF- α .(Ridker, Rifai et al. 2000; Cesari, Penninx et al. 2003) IL-6 promotes atherosclerosis, by stimulating the endothelial synthesis of cellular adhesion molecules, procoagulant effects, and stimulation of the hepatic synthesis of CRP.(Ridker, Rifai et al. 2000; Cesari, Penninx et al. 2003) Although we did not observe significant results with CRP and TNF- α , the current evidence is substantial enough to lay weight to the claim that diet modulates inflammation and through this process and thus influences chronic diseases, including cardiovascular diseases.

This investigation has both strengths and limitations. Strengths include its longitudinal design using non-diabetic participants with MetSynyn. Most of the previous findings are from cross-sectional studies using healthy populations or those with diabetes. Another strength is the use of multiple of 24HR at each time point. The 24HR method is the most accurate method for measuring macronutrient and micronutrient intakes, owing

to its ability to assess intake of foods, such as spices, that are not commonly found on structured instruments such as food frequency questionnaires. This is the first intervention study in which DII has been used to examine associations with metabolic and inflammatory biomarkers. All previous studies examining DII have been used cross-sectional, case-control or cohort designs.(Shivappa, Steck et al. 2013; Hebert, Shivappa et al. 2014; Wirth, Burch et al. 2014; Wood, Shivappa et al. 2014) Our findings further stress the importance of diet rich in components such as fiber, magnesium and other anti-inflammatory components for improving markers of insulin resistance and inflammation as a potential mechanism for reducing that can reduce the incidence of MetSynyn and, subsequently, other chronic diseases such as CVDs and cancers. Limitations include a small sample size and that results are generalizable to this group of primarily European America, obese, educated participants. Even though baseline sample size was 240 and repeated measurements were obtained, the final analytic dataset had 237 subjects with complete information on diet, biomarkers and covariates. Many of the results that were not significant in this study, including on CRP, might have been statistically significant had the sample size been larger.

Conclusion:

Results from this study suggest that eating a high-fiber diet high in anti-inflammatory properties can reduce DII and may decrease chronic disease risk by reducing circulating levels of both metabolic and inflammatory biomarkers such as insulin, glucose, HOMA-IR and IL-6. DII could serve as an important tool that could help people to understand whether the diet they are consuming is healthy and influence

them to take steps to improve their diet. The logical next step is to check the applicability of DII in other intervention trials.

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Table 6.1 Baseline description of characteristics across tertiles of DII, all subjects pooled irrespective of intervention status, , CAN DO Study, Worcester, Massachusetts, 2009-2014.¹ (n=240)

	Tertile 1 (<-0.73)	Tertile 2 (-0.73 to 1.19)	Tertile 3 (>1.19)	P-value ¹
Continuous variables characteristics²				
Age (years)	51.8±9.6	52.0±9.6	52.1±10.7	0.83
BMI (kg/m ²)	34.7±2.6	34.9±3.3	35.5±2.8	0.08
Systolic blood pressure (mm of Hg)	134.7±9.5	136.7±11.5	135.8±7.7	0.46
Diastolic blood pressure (mm of Hg)	79.8±7.1	79.9±8.0	81.5±10.7	0.23
HDL-C (mg/dl)	48.3±10.8	47.9±10.3	47.4±9.3	0.58
Triglycerides (mg/dL)	158±72.4	155.4±91.1	140.2±67.6	0.14
Fasting plasma glucose (mg/dL)	98.6±11.5	100.1±13.0	99.2±12.8	0.73
Fasting plasma insulin (μU/mL)	14.2±12.4	13.7±12.4	16.1±13.6	0.34
HOMA insulin resistance	3.5±3.3	3.4±3.1	4.1±4.0	0.29
CRP (mg/l)	3.9 ±4.4	4.4±4.4	5.5±7.6	0.10
IL-6 (pg/ml)	2.0±1.1	3.1±5.6	3.6±4.7	0.03
TNF-α (pg/ml)	2652.5±622.7	2608.9±539.6	2924.1±1227.9	0.05
Total fiber intake (mg/day)	24.9±6.0	18.5±5.6	13.6±3.6	<0.0001
Total energy (kcal/day)	2275±702.1	1823.3±499.8	1541.3±454.3	<0.0001
Physical activity (MET: h/day)	28.6±4.6	27.5±3.8	27.0±3.0	0.01
Categorical variables characteristics				
Females	46 (60.5)	58 (74.4)	62 (81.6)	0.01
White	71 (93.4)	71 (91.0)	61 (80.3)	0.19
Educate				0.83
High school or less	9 (13.8)	13 (15.8)	11 (13.2)	
Bachelor's degree or less	37 (56.9)	49 (59.8)	54 (65.1)	
Graduate/professional	19 (29.2)	20 (24.4))	18 (21.7)	
BMI categories				0.38

BMI (30–34.9 kg/m ²)	36 (47.4)	36 (46.1)	31 (40.8)	
BMI (≥35.0 kg/m ²)	39 (51.3)	37 (47.4)	43 (56.6)	

HDL-C: High-density lipoprotein cholesterol; HOMA: Homeostasis model of assessment; BMI: Body mass index;

¹*P* values are for any difference across the quintiles of magnesium intake using ANOVA, or χ^2 test as appropriate;

²All continuous variables values are mean \pm standard deviation;

Table 6.2 Association between DII and metabolic biomarkers of insulin resistance according to a linear mixed model among non-diabetic individuals with MetSyn, CAN DO Study, Worcester, Massachusetts, 2009-2014.¹

Continuous outcomes	Beta estimates ²	95% C.I.	Beta estimates ³	95% C.I.
Insulin (μU/mL)				
Continuous	0.02	-0.002, 0.05	0.03	0.00002, 0.06
Tertile 2	0.08	-0.04, 0.20	0.07	-0.05, 0.19
Tertile 3	0.14	0.005, 0.28	0.15	0.01, 0.28
Glucose (mg/dL)				
Continuous	0.004	-0.0002, 0.008	0.006	0.002, 0.01
Tertile 2	0.01	-0.007, 0.03	0.02	-0.003, 0.03
Tertile 3	0.02	-0.0002, 0.04	0.03	0.009, 0.05
HOMA-IR	0.13	0.04, 0.21	0.11	0.02, 0.21
Continuous	0.06	0.04, 0.07	0.05	0.03, 0.07
Tertile 2	0.09	-0.04, 0.22	0.08	-0.05, 0.22
Tertile 3	0.16	0.02, 0.30	0.18	0.03, 0.32

¹ Estimated by PROC MIXED in SAS; ² Adjusted for group and time-point; ³ Adjusted for gender, race/ethnicity, BMI category, triglycerides, group, and time-point.

Table 6.3 Association between DII and inflammatory markers according to a linear mixed model among non-diabetic individuals with MetSyn, CAN DO Study, Worcester, Massachusetts, 2009-2014.¹

Continuous outcomes	Beta estimates ²	95% C.I.	Beta estimates ³	95% C.I.
Hs-CRP (mg/l)				
Continuous	0.002	-0.03, 0.03	0.05	-0.005, 0.11
Tertile 2	0.09	-0.03, 0.23	0.11	-0.02, 0.24
Tertile 3	0.03	-0.11, 0.18	0.04	-0.11, 0.18
IL-6				
Continuous	0.03	0.008, 0.05	0.03	0.008, 0.05
Tertile 2	0.08	-0.01, 0.18	0.08	-0.02, 0.18
Tertile 3	0.14	0.02, 0.25	0.13	0.02, 0.25
TNF- α				
Continuous	0.002	-0.004, 0.01	0.003	-0.005, 0.01
Tertile 2	0.02	-0.01, 0.05	0.03	-0.01, 0.07
Tertile 3	0.007	-0.02, 0.04	0.004	-0.04, 0.05

¹ Estimated by PROC MIXED in SAS; ² Adjusted for group and time-point; ³ Adjusted for gender, race/ethnicity, BMI category, triglycerides, group, and time-point.

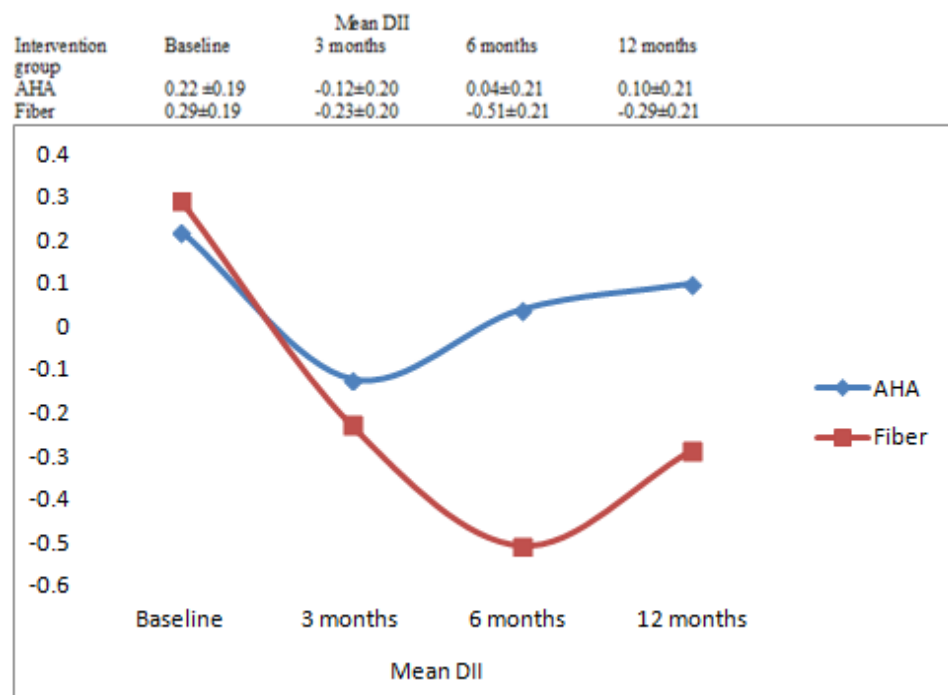


Figure 6.1 Mean DII across time points for the two intervention groups.

CHAPTER 7

Summary

Modifying and Refining of Dietary Inflammatory Index: A Learning Experience

The Dietary Inflammatory Index (DII) was developed as a novel tool to assess the inflammatory potential of individuals' diets. While the primary goal was to use the DII as a research tool which could be used widely across a variety of different kinds of studies using different dietary assessment methods, we also saw the potential for it to help educate individuals learn about the inflammation-modulating effect of the foods that they eat and this could, in turn, help them to adopt a healthier diet.

The earlier version of DII, which was developed by Cavicchia et al., (Cavicchia, Steck et al. 2009) had certain methodologic shortcomings that are described in Chapter 2. In the original DII, literature review-based scores were multiplied by individuals' actual intakes of food parameters, with no attempt to relate to any external standard of intake. One major issue with this version of the index was that this approach was sensitive to the units of measurement. For example, μg and mg differ by three orders of magnitude and some parameters, such as vitamin A and β -carotene, had to be divided by 100 and others, such as omega-3 and omega-6 fatty acids, multiplied by 10 in order to place them in reasonable range so as not to over- or under-estimate their influence on the overall score.

The new DII is improved in a number of ways. First, an improved scoring system has been applied to the 45 “food parameters,” consisting of whole foods, nutrients and other bioactive compounds derived from a much larger literature review. Second, 11 food consumption data sets from around the world were identified that represent a range of human dietary intakes that serve as the “referent” population database to provide comparative consumption data for these 45 food parameters.(McLennan W. 1995; Bahorun, Luximon-Ramma et al. 1996; Pan, Kao et al. 1999; Health. 1999.; Parnell, Wilson et al. 2001; Nakamura, Tajima et al. 2002; Henderson, Bates et al. 2004; Chun, Chung et al. 2007; Barquera, Hernandez-Barrera et al. 2009; Shim YJ 2009; Ferrucci, Daniel et al. 2010; 2011; Knudsen, Gille et al. 2011) Third, a percentile scoring system was devised that serves as the actual values against which individuals’ intakes are multiplied in order to derive each individual’s DII score. In an effort to address these issues and to update the literature search from 2007 to 2010, I began to work on this project as part of my graduate assistantship. Around this time I was looking for different projects to work on apart from the one I was already working on. When I was given a briefing by my academic advisor on this project (who also became my dissertation advisor), I had not yet taken any nutritional epidemiology classes and knew almost nothing about any of the available dietary indices; although I did not understand the entire process (it would be many months before its full complexity was revealed) I did understand that it was pretty complicated. Indeed, the initial work was focused on the principles of what we were setting out to do. It would take a long time in many discussions with Dr. Hébert, Dr. Susan Steck, Dr. Jim Hussey, and Tom Hurley to work out the entire scoring algorithm and the validation.

Despite that I knew that it would take many discussions and lots of work over what I thought might be a long time, the thought of developing a novel dietary index which would capture interest of researchers around the world intrigued me and I said yes to the project immediately. Dr Philip Cavicchia, who had worked on the previous edition of DII, explained to me what needs to be done in terms of updating the literature and he also briefly about the validation study. It was when I started working on the project that I realized the enormity of this task. It was herculean because of the sheer intensity of work wherein I would be required to screen close to 6000 articles, review the selected articles, and then enter the relevant information such as: the direction of observed associations, whether it was significant or not, name of the first author in to an Access database and finally printing the article to keep for records. Although it was a daunting task, I knew if we could accomplish what we had set out to achieve, all the effort which I would be putting be worth it.

The process of literature review, though time consuming, provided me an opportunity to learn a lot about the properties of foods and their constituents and their relation to inflammatory markers we were using for DII calculation. During this process we made many changes such as scoring an article repeatedly if association were observed between food parameter and multiple inflammatory markers. All these changes were made after careful consultation with Drs. James Hebert, Susan Steck and Jim Hussey, and Tom Hurley. Once we agreed on all the steps and the scoring algorithm for DII was developed, the next step was to do validate it with a inflammatory biomarker as outcome. Construct validation was done using data from the Seasonal Variation of Blood Cholesterol Study (SEASONS) with the inflammatory marker hs-CRP as our construct

validator (outcome). Briefly, SEASONS was a prospective observational study. A total of 641 healthy participants were followed for 1 year, with data obtained at baseline and then every 3 months, within a 3-week window on either side of the individual's quarterly appointment date, to the 1-year anniversary point (total of five assessments). Eligibility criteria included being a resident of Worcester County (MA, USA), age 20–70 years and having telephone service. Study participants were not taking cholesterol-lowering medications (e.g. statins) and were not actively on lipid-lowering or weight-control diets, did not have possible causes of secondary hyperlipidemia, had not been diagnosed as having CHD, and were free of life-threatening illness. Individuals were recruited between December 1994 and February 1997 and enrolment occurred throughout the calendar year. The results of the validation were indeed impressive; this new version of the DII that we developed appeared to fare better than its predecessor! The DII was able to predict hs-CRP as a dichotomous variable in with different two dietary assessment tools (24-HR and 7DDR) (Shivappa 2013; Shivappa, Steck et al. 2013).

SEASONS was conducted in the New England region and participants were predominantly European American. Furthermore, the results were significant for only the dichotomous CRP variable. Therefore, in order to determine the validity of DII in study with greater racial diversity I started exploring datasets which had information on multiple races, had dietary data from a variety of sources, and also had information on CRP. While doing this search that I came across NHANES which is the nationally representative cross-sectional study conducted every year, in which data are collected from different regions of the US with participants selected to represent the racial makeup

of the country. The NHANES also had information on diet which was collected through 24HR, and CRP.

I proposed this idea of using the NHANES dataset as the basis for my Aim 1 to my committee members and upon discussion it was accepted. I decided to construct a dataset using all relevant information from NHANES 2005-2010 and while importing data from NHANES 2007-2008, I realized that codes have been made available for the calculation of HEI-2005 on the CDC website for this particular year, I then realized that it would be possible to calculate HEI-2005 scores for the entire NHANES 2005-2010 dataset and conduct analyses similar to what we had done for the DII and then we could compare the results. This comparison became a sub aim Aim 1. Significant results were observed for CRP both as continuous log-transformed variable and as a dichotomous variable categorized based on the cut-off of >3 mg/l (which, as noted, is the AHA cutpoint for “high” risk). Significant associations also were observed with HEI-2005; however, the results were slightly better for DII with a predictive ability for CRP >3 mg/l of 6% higher for DII relative to the HEI.

Because we wanted to ensure that the DII had relevance for human health beyond inflammatory markers, we decided that the next step was to test DII with health outcomes. Specifically, we wanted to see if the DII could predict outcomes previously shown to be associated with inflammation and diet. In this regard I started exploring NHANES to see if there was a prospective component with health outcomes; this is when I came across NHANES III cohort study. The NHANES III study was conducted between 1988 and 1994. Data provided by participants were subsequently linked, by probabilistic matching, with National Death Index records through 31 December 2006 by the National

Center for Health Statistics (NCHS). I proposed to use this study to explore the association between DII and mortality outcomes; this became dissertation Aim 2. Initially I wanted to look at all-cause mortality, colorectal cancer, breast cancer and prostate cancer mortalities. However, when I began working on setting up the dataset I realized that there were not enough site-specific cancer deaths. After discussing this issue with my academic advisor it was decided that I look at all-cause mortality, overall cancer mortality, digestive-tract cancer mortality and CVDs mortality. There were sufficient numbers of outcomes for each of these categories. DII was found to be strongly associated with all-cause mortality, overall cancer mortality, digestive-tract cancer mortality and CVDs mortality.

Next, I wanted to understand how DII would fare in an intervention study. My third aim explored the association between DII and inflammatory and metabolic biomarkers in the CAN DO intervention study. In this study 234 participants with MetSyn and without diabetes were recruited, deemed to be eligible, and randomized into one of the two dietary interventions: a high-fiber diet or the American Heart Association (AHA) diet. In the high-fiber diet condition, participants received instruction to achieve a daily dietary goal of ≥ 30 g fiber intake from a variety of food sources. Patients in AHA diet group were instructed to make dietary changes addressing both macro- and micronutrients as recommended by the AHA 2006 dietary guidelines. The inflammatory markers were CRP, TNF- α and IL-6; and metabolic biomarkers were blood glucose, blood insulin and HOMA-IR. The decrease in DII across time points was more appreciable for “fiber” group compared to “AHA” group. DII was found to be marginally associated with CRP and TNF- α (<0.10) and strongly associated with IL-6 (<0.05) and

was strongly associated with all the metabolic biomarkers (<0.05). Table 7.1 describes the summary statistics of DII in all the three aims.

Current work and suggestions for future research

All of the aims encompassed by my dissertation relate to participants to US. In order for DII to achieve our overarching goal of developing an index that can be used anywhere, in any population, using any dietary assessment it has to be tested in studies from countries from around the world, and in a variety of cultural contexts. With the exception of the 7DDR in the SEASONS study, the dietary assessment tool used in my entire dissertation Aims is the 24HR. While 24HR is the gold standard dietary assessment tool and is the most accurate method for measuring macronutrient and micronutrient intakes, owing to its ability to assess intake of foods, such as spices that are not commonly found on structured instruments it is an expensive measurement technique that is beyond the means of most epidemiologic research studies. Also, the outcomes explored in my dissertation are limited; therefore, I think it would be interesting to explore other outcomes including incidence of specific cancers such as colorectal, prostate, and pancreas.

In large part owing to the success of the DII thus far, more than 100 DII-related collaborations have been established with research groups around the world including Karolinska Institute, IARC, University of Melbourne, the Whitehall Study group, and several US government agencies (e.g., NIH and NIOSH). We are using DII in several cohort studies in the world, including the EPIC cohort, Women's Health Initiative, the Multiethnic Cohort, the Iowa Women's Study, the NIH-American Association of Retired

Persons (NIH-AARP) Diet and Health Study, and the Southern Community Cohort Study. We also are developing collaboration with the nutrition group at NASA, who has expressed interest in using DII to determine the inflammatory potential of the diets prescribed to astronaut trainees. In addition to these collaborations, physicians and nutritionists at University of Sao Paolo, Brazil are making dietary recommendations to patients suffering from psoriasis and arthritis based on the findings from the DII. Currently we have published seven DII-related manuscripts; one is in press, 12 are under review and several in various stages of development. The dietary assessment tool in all these studies is either 24HR or food frequency questionnaire (FFQ) and some include both. Subsequent to, or along with, all of these collaborative efforts, we also plan to work on making DII available to clinicians, nutritionists and ordinary people in the form of a simple mobile application.

Problems faced and things learnt along the way. The dissertation is a scientific document that resulted from literally thousands of hours of work. In this process of refining ideas, collecting data, producing results and drawing inferences I have grown as a scientist. At the urging of my major professor, Dr. James Hébert, I have sought to describe how this influenced me. My goal in doing this is two-fold: 1. To record the process and 2. To provide documentation that may be useful to future doctoral students.

Develop short-term goals: Faced with having to screen all articles published from 2007-2010 that examined the association between each of the 45 food parameters and each of the six inflammatory markers I thought it was a Herculean task. This was reinforced in discussions with Dr. Cavicchia in which he described the amount of time an

effort he invested in developing the first DII. His descriptions kept coming to my mind when I saw the number of articles I would have to review and add to what he had done.

I began without a clear working plan – which was fine for familiarizing myself with the literature, but did not optimize efficiency. The other projects that I was assigned as part of my graduate assistantship were very demanding; so, I found myself concentrating more on those projects. In order to get the DII project done I decided to develop short-term goals wherein I took each food parameter at a time and searched the literature to identify the articles I had to screen. I then set myself a timeline depending on the number of articles and worked up a schedule to complete the screening and review within my prescribed timeline. This plan and strategy allowed me to stay motivated and to work efficiently. In some instances, I had to work through the night to meet my self-imposed deadline. Of course, there were times when I could not meet my deadline due to commitments to other projects; however, these “misses” were few and far in between and my ability to estimate the time needed improved as the project continued and my efficiency increased. Also, updating Dr. Hébert about my plans and progress also improved efficiency.

Patience is a virtue: There was only a short time between my beginning to work on this project and Dr Philip Cavicchia, who led the development of the original DII, left the Cancer Prevention and Control Program (CPCP). Though he had expressed no interest in continuing to work on the DII, he really helped me with understanding the different processes involved in what he did. While reviewing the articles and scoring them I would get doubts and questions; for example, what should be done if in an article more than one inflammatory marker were studied in relation to the food constituent?

Should I send the questions to professors through email, or should I just enter their office and ask them? At first, I was very hesitant to bother Dr. Hébert and the other team members. So I started off by sending emails with the questions and I would get frustrated if I did not receive a response quickly. Though Dr. Hébert was usually busy dealing multiple projects, classes, grading, publications, grants etc., it became clear that the DII was high on his list of priorities and if DII was one among the several projects for my committee members, while it was my main project – it still was accorded very high importance among all of the things on which the entire Cancer Prevention and Control Program was focused.

Over time, I became more patient and strategic in how I conducted my work and started approaching this problem in a different way. If I had questions I would write them down and accumulate them and then set up a meeting with all the concerned researchers to discuss them and then finally come out with solutions.

Begin Early: Once the DII was developed and the papers on developing and validating the method were published, I started exploring other studies in which DII could be used. I spent a lot of effort and time in contacting researchers in countries from around the world, in drafting proposals for studies such as Whitehall and EPIC cohorts, in doing DII calculation and working on analyses and manuscripts for other studies. Indeed, because of all this we have been able to establish quality collaborations and will be able to publish many relevant manuscripts based on the DII. Though all of this work is related to the DII, devoting time to this process caused me not to concentrate on my dissertation. As a result, I had to complete the entire analyses for all the three aims and the write up the analyses within a short time. Fortunately, all of the other DII-related work has caused

me to become highly organized and very efficient. All of the collaborative work that I had undertaken has allowed me to develop “boiler plates” for methods that we would use across a variety of study designs and endpoints using the DII as the exposure and I worked on this and modified it while writing up my dissertation. Despite all of the improvements in my work ethic, I still feel that I left it too late; so, I would recommend to future students that they begin working on their dissertation projects early. Once your proposal defense is completed dedicate some time each week to your dissertation work. This will avoid the undue work load and pressure towards the end. In working with my very busy faculty committee members, I also know that this issue of time management is a perennial problem, even for very successful people – so, I also have learned not to be too hard on myself.

Mistakes are common, it is important to learn from them: Before working on the DII project, I had very limited exposure to research and there are several mistakes I committed during this journey. When I started off I was not aware of the importance of documentation, so I was not documenting the decisions taken during the meetings and was also not saving the SAS codes after running the analyses, these resulted in a lot of confusion and problems. Dr Hebert made me understand the importance of this process and I started documenting and saving each completed step. When I started I did not have the fundamental skills that I would develop later; e.g., how to format tables, how to present results. All of these things I have learnt over the course of time and though I am still not perfect, I have become very proficient in doing all of these things.

Enjoy your work and take breaks: There were times while working on the DII development when I would get bored reading the articles, I wanted to do some other work

or take breaks. Fortunately for me I was also working on another project, an intervention trial. This allowed me to take my mind away from the DII project when required. Also, I took other breaks; for example, once I completed scoring all the eligible articles, then next step was to do the validation and before I began this process I took a break for a few days, by going for a vacation and started fresh on the validation section after returning. Another important component that was very important and that really kept me motivated During the entire process I had the constant encouragement from my advisor. Whenever I would give Dr. Hébert an update he would say “Excellent, keep up the good work.” These words would stay with me for a while, finding them very helpful because, in the first part he appreciated me by saying “excellent” and in the second, he advised me to keep going and continue to do hard work. This would continuously motivate me. It is a result of this that I was able to establish these many collaborations. Hence, it is important not to get bogged down by the work load; it is definitely a must to take breaks once in a while and look out for words of encouragement from your advisors which can motivate you.

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Table 7.1. Summary statistics for DII from the three aims.

Dietary Inflammatory Index (DII)	Aim 1 (N=12811)	Aim 2 (N=12438)	Aim 3 (N=567)
Minimum	-4.95	-5.64	-5.60
Median	1.15	0.96	-0.08
Maximum	4.95	4.83	4.73
Mean	0.94	0.72	-0.05
Standard deviation	1.80	2.20	2.09

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