8-23-2016

Association of the Dietary Inflammatory Index with Metabolic Syndrome in the National Health and Nutrition Examination Survey (2001-2006)

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B.S., Penn State University, 2007

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Public Health

At the

University of Connecticut

2016

APPROVAL PAGE

Master of Public Health Thesis

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2016

ACKNOWLEDGEMENTS

We thank Rong Wu, MS and Masteneh Sharafi, PhD for their work in converting information about the dietary inflammatory index from scientific papers into a statistical algorithm, assembling the needed variables from the NHANES dataset, and calculating dietary inflammatory index scores of NHANES participants.

Abstract

Metabolic syndrome currently affects one third of adults in the U.S. and has been associated with a variety of chronic diseases that pose a burden to the nation. [1,2] In the nationally representative NHANES dataset (2001-2006), dietary inflammatory index scores were found to significantly predict metabolic syndrome outcome among individuals above the age of 50 (OR=1.088; 95% CI=1.014-1.167; p=0.0184). Individuals older than 50 years of age who consume diets very high inflammatory properties were found to be 2.14 times more likely to have metabolic syndrome than those who consume a diet with very low inflammatory properties. This study supports the hypothesis that there is a link between diet and metabolic syndrome, possibly through inflammatory mechanisms. Future research to establish causality between the dietary inflammatory index and metabolic syndrome could lead to further developments in the utilization of the DII as a tool for dietary intervention of this syndrome.

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Introduction

Metabolic syndrome (MetS) is a cluster of risk factors that have been associated with development of type II diabetes, cardiovascular disease, and atherosclerosis.[1] Those with MetS have twice the risk of having a stroke or heart attack as those who do not.[2] Currently, one third of adults in the US (34%) are estimated to have MetS.[2] A plethora of studies have been conducted in the attempt to delineate the lifestyle factors that contribute to this syndrome in order to reduce its burden on society.[1]

MetS and some of its associated risk factors have been linked with low-grade chronic inflammation and certain diets (e.g. the Mediterranean diet, the Healthy Eating Index, vegetarian diets, Western dietary patterns).[1] The relatively new dietary inflammatory index (DII) is a research tool being used in the assessment of the effect of pro-inflammatory food intake on risk of chronic diseases and conditions including MetS.[3] The purpose of this study is to assess whether inflammatory properties of the diet, determined by a DII score, is associated with incidence of MetS using a large population in the National Health and Nutrition Examination Survey (NHANES) 2001-2006.

Background and Significance

Metabolic Syndrome

MetS is defined as the presence of a combination of risk factors that increase one's chance of developing atherosclerotic cardiovascular disease.[4] MetS may also increase one's chances of developing type II diabetes, as well as a multitude of other conditions including fatty liver and sleep apnea.[4] MetS is not a defined disease but is a cluster of risk factors that are commonly found together and that indicate increased risk of atherosclerotic disease.[4] A positive diagnosis of MetS requires at least three out of five components present: abdominal obesity, high triglyceride levels, low levels of high-density lipids (HDL), hypertension, and elevated blood glucose.[5] It is possible that some individuals with MetS have unrelated causes for each of these risk factors, while others have this cluster of risk factors due to a related underlying cause.[4] Those with the syndrome are twice as likely to develop cardiovascular disease over the next five to ten years and are five times as likely to develop type II diabetes as those without.[5] MetS

has been associated with chronic inflammation and increased risk has been linked to dietary choices, particularly those of a Western-style diet rich in saturated fat and cholesterol.[1,4,6]

Threshold values of abdominal obesity vary according to ethnic groups, sex, and populations.[5] This study uses one of the two abdominal obesity thresholds established for the United States for males and females separately; the level being used having a higher cutoff point indicating substantially higher risk of cardiovascular disease.[5]

C-reactive Protein

Presence of chronic low-grade systemic inflammation can be measured through several markers in the blood such as: C-reactive protein (CRP), interleukin (IL-6), homocysteine, and fibrinogen.[7] Serum CRP is a highly sensitive marker of inflammation. CRP levels have been significantly and positively associated with metabolic syndrome, all five components of metabolic syndrome individually, and with increasing levels as the number of components increase in an individual.[8-10] CRP has also been significantly and positively associated with incidence of diabetes and cardiovascular disease.[8,9,11] The NHANES utilized the high-sensitivity CRP (hs-CRP) assay, which can detect levels down to 0.03 mg/dL and is one of the best candidates for measuring inflammatory states.[12,13] Levels of hs-CRP are considered clinically elevated at levels above 1.0 mg/dL, which typically reflect acute inflammation such as an active infection.[12] In accordance, most studies have shown that 95% of individuals have hs-CRP values below 1.0 mg/dL.[12] Values above 0.3 mg/dL have been found to indicate elevated-risk for cardiovascular disease among individuals, while values of 0.1 to 0.3 mg/dL indicate average risk and values less than 0.1 mg/dL indicate low risk.[12]

Dietary Inflammatory Index

The dietary inflammatory index (DII) is a tool that was recently developed to assess the inflammatory nature of a diet.[3] The index was formulated based on a review of literature that looked at past associations between dietary nutrients and inflammatory potential.[3] From this, a weighted score was assigned to each nutrient, based on the degree of effect, and an algorithm was developed to assign one overall inflammatory score to an individual's diet.[3] The DII thus ranks one's diet "on a continuum from

maximally anti-inflammatory to maximally pro-inflammatory." [14] Scores above zero are increasingly pro-inflammatory, whereas scores below zero are indicative of a diet with lower inflammatory potential. [3]

The DII can be used in studies where nutrient data is collected, for example through 24-hour dietary recalls, 7-day dietary recalls, or food frequency questionnaires. Nutrients that have shown to promote low inflammatory levels include: complex carbohydrates, n-3 PUFAs, fiber, moderate alcohol intake, vitamin E, vitamin C, beta-carotene, and magnesium." [15] Diets high in fruits and vegetables, omega-3 fatty acids, whole grains, and that are low in saturated and trans fats have been associated with lower inflammation. [1,7,16] Consuming the Mediterranean diet and a diet adhering to guidelines of the Healthy Eating Index (HEI) have also been shown to reduce one's odds of developing MetS. [1] Other foods and nutrients associated with lower CRP concentrations include legumes, nuts, and low-fat dairy products. [17] Animal protein, on the other hand, has been associated with higher levels of inflammation. [15]

Unlike other diet indices, the DII was developed in relation to outcome measures (i.e., circulating biomarkers of inflammation), and hence, it is the only index to date linked to biological processes and has been validated in numerous studies. [3,7,14,18] In the Seasonal Variation in Blood Lipids (SEASONS) study, for example, it was found that lower DII index scores, indicating more anti-inflammatory properties, were significantly associated with decreased hs-CRP levels. [3] Significant findings were only seen when hs-CRP was analyzed as a dichotomous variable as opposed to as a continuous variable, which indicates that a non-linear relationship may be present between hs-CRP and diet. [3] It was also further validated in a study with postmenopausal women to associate DII scores with hs-CRP, IL-6, and a tumor necrosis factor alpha receptor 2 (TNF-alpha). [14] The validation of the DII through these studies shows that this index can be used to further examine associations of the inflammatory nature of diets with chronic diseases in other studies. [14] The DII has thus far been used in studies to show associations between a diet's inflammatory potential and colorectal cancer, prostate cancer, pancreatic cancer, breast cancer, asthma, and cardiovascular disease. [19-26]

Validation studies have confirmed that the DII is associated with several inflammatory markers, particularly hs-CRP. [3] Studies have also shown that inflammatory markers have been associated with

MetS.[8] It is believed that diet can impact the development of MetS and consequent cardiovascular diseases by producing an increased amount of pro-inflammatory cytokines and a reduced amount of anti-inflammatory cytokines.[16]

Inflammatory biomarkers, particularly the cytokines TNF-alpha and IL-6, are produced by adipose tissue.[8] TNF-alpha also impairs insulin functions. Since both insulin resistance and central adiposity are determinants of MetS, a strong relationship between inflammatory biomarkers and MetS has been established.[8]

MetS has been examined in relation to a diet's inflammatory index in four studies with divergent findings. The Buffalo Cardio Metabolic Occupational Police Stress (BCOPS) study considered the association between a diet's DII and MetS among the police workforce in Buffalo, New York.[27] This cross-sectional study did not find a significant association between MetS and the DII.[27] It did, however, find an association between higher DII scores and glucose intolerance.[27] This study was applied to a specific, relatively small subset of the population and may have found no significant association MetS due to lack of power or components particular to that population. It is possible that analysis of this association with a larger, more varied population could yield significant results.

Alkerwi *et al.* examined the association between a diet's DII and MetS among European adults in the Observation of Cardiovascular Risk Factors in Luxembourg study.[28] This cross-sectional study did not find a significant association between MetS and the DII. This study also did not find an association between hs-CRP levels and the DII, which has been found in multiple other studies. This lack of association could be due to multiple factors, including a healthier population and lack of various food components in the food frequency questionnaire used that would have been incorporated into the DII.[28]

A study authored by Neufcourt *et al.* used the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study to examine the association between a diet's DII and MetS outcome among French adults.[29] This was a prospective cohort study where MetS was not present among participants included at baseline and was assessed at the end-of-study follow-up. A positive and significant association was found where increasing DII scores were indicative of increased risk for MetS

(OR=1.39, 95% CI=1.01-1.92, p=0.047). Authors state that the finding is marginally significant and should be interpreted with caution. Participants were screened in a manner that yielded a very compliant final pool, which lowers external validity. [29]

In a cross-sectional study by Sokol *et al.*, the association between a diet's DII score and MetS was examined among individuals from the Polish-Norwegian Study. [30] No significantly increased risk of MetS was found among those who consumed a more pro-inflammatory diet, although a significantly reduced risk of MetS among females in the highest DII quartile was found in comparison to females in the lowest DII quartile. Authors of this study believe that the cross-sectional nature of the study may have contributed to the harmful effects seen of an anti-inflammatory diet, where women with poorer health may have consequently altered their diets in a healthy way. This study used an abbreviated 55-question food frequency questionnaire, which may have lowered the study's ability to detect dietary differences. [30]

Research Objective

We hypothesized that MetS status would be significantly associated with DII scores. This was a two-tailed hypothesis. The inflammatory potential of one's diet was the independent variable and was measured through the DII. The DII was calculated using the nutrient composition of individual diets recorded in NHANES through Day 1 of the 24-hour dietary recall. The calculations were done using an algorithm formulated by Cavicchia et al. [3] MetS was the dependent variable and it was measured using the NHANES records of waist circumference, triglyceride levels, HDL levels, fasting plasma glucose levels, and blood pressure levels. [31] The null hypothesis was that one's metabolic syndrome status has no association with one's dietary inflammatory index score.

Methodology

Overview

A secondary data analysis was conducted using cross-sectional data, looking at the association between dietary inflammatory index scores and metabolic syndrome status. Quantitative data was used from the NHANES datasets from years 2001-2006. NHANES collected nationally representative data using a tiered randomized sample section procedure. It is hypothesized that the inflammatory properties

of one's type of diet, as indicated by the dietary inflammatory index, are a predictor of MetS (see Figure 1 below). Presence of chronic inflammation is hypothesized to be a partial mediator, and a result in part, of a pro-inflammatory diet. Logistic regression analyses were conducted to determine if DII scores significantly predicted MetS status. Possible confounders were controlled for in the analysis. We additionally examined if the relationships between DII and hs-CRP, and DII and each of the five MetS components were significantly associated.

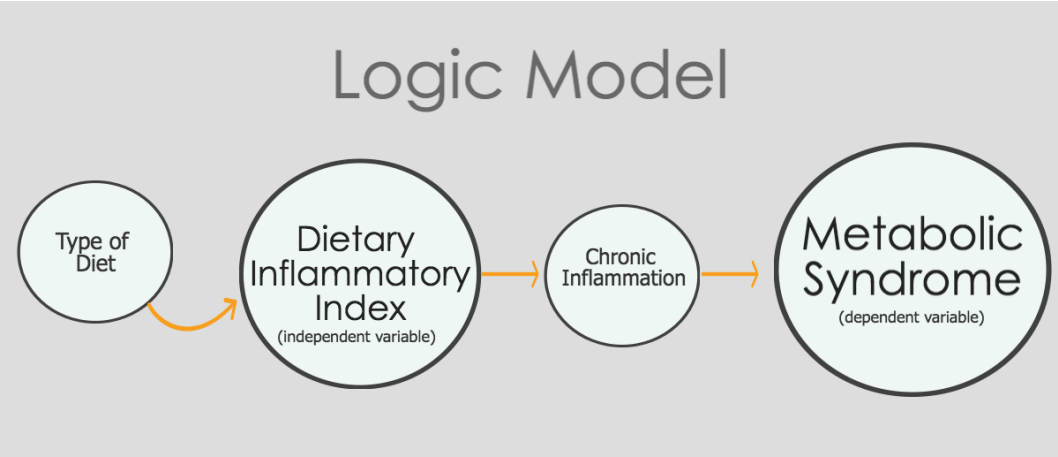

Figure 1. Logic model for the relationship between dietary inflammatory index and metabolic syndrome.

Metabolic Syndrome Clinical Definitions and Measures

The clinical definition for MetS is outlined in a joint scientific statement by the American Heart Association, the National Heart, Lung, and Blood Institute, the International Diabetes Federation Task Force on Epidemiology and Prevention, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity.[5] These state that three out of five risk factors must be present in an individual for diagnosis. The five risk factors include: central obesity, hypertension, low HDL cholesterol levels, high triglyceride levels, and glucose intolerance.[4] The clinical cut-off points for measures of each of the above risk factors, respectively, are as follow: waist circumference greater than or equal to 102 cm for men or greater than or equal to 88 cm for women; systolic blood pressure greater than or equal to 130 mm Hg or diastolic blood pressure greater than or equal to 85 mm Hg; a concentration of HDL cholesterol less than 40 mg/dL for men or less than 50

mg/dL for women; a concentration of triglycerides greater than or equal to 150 mg/dL; and fasting plasma glucose levels greater than or equal to 100 mg/dL. [4]

Measures for all five risk factors of MetS were collected and recorded in the NHANES dataset. [32] All needed measurements were collected in the NHANES mobile examination center (MEC) by trained NHANES staff who were using standard protocols. A physical examination component measured waist circumference as well as systolic and diastolic blood pressure on the brachial artery. Blood samples were collected from all participants by a trained NHANES phlebotomist. Blood samples were shipped from the MEC to laboratories elsewhere for assays. Triglycerides, hs-CRP, and HDL levels were measured from blood serum samples. Fasting glucose levels were measured from blood plasma samples.[32]

Other explanatory variables incorporated into analyses in this study were collected from interviews in the MEC, including sex, age, ethnicity, education level, history of diabetes, and smoking status. [32] The physical activity variable was calculated from self-reported information collected in the household interview. [32] This included questions about intensity level of activity, average duration of activity, and number of times of activity over the past 30 days. [32] A dichotomous variable was created where individuals either met American College of Sports Medicine (ACSM) guidelines or did not meet guidelines. To meet ACSM guidelines, an individual must have performed moderate activity at least 20 times over the past 30 days for an average duration of at least 30 minutes, or must have performed vigorous activity at least 15 times in the past 30 days for an average duration of at least 20 minutes. [33] Components for BMI, height and weight, were collected during the physical examination component of the MEC examination.[32]

Dietary Inflammatory Index Measures and Methods

The dietary inflammatory index is a tool that analyzes an individual's diet and assigns an inflammatory score to this diet. Scores are on a continuum where values above 0 indicate pro-inflammatory properties and values below 0 indicate anti-inflammatory properties. [3] The tool first assigns a score to foods that were judged to have positive or negative effects on inflammation levels. These scores were developed by conducting a literature search of articles between 1950 and 2010 that showed

relationships between foods and one of six common inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNFα, and CRP).[3,34] A total of 1943 articles were reviewed.[34] If effects were found to be pro-inflammatory, the article was assigned a score of -1.[3,34] If effects were found to be anti-inflammatory, the article was assigned a score of 1.[3,34] A score of 0 was assigned to the article if no significant effects were found between a food component and inflammatory markers.[3,34] In assigning a score to food components for the tool, scores were weighted according to study type and design, and scores were adjusted according to the total number of articles that associated this food with one of the six inflammatory markers.[3] Also, food components that were associated in less than ten articles were excluded from the tool.[3] Scores for each individual considers the scores of each food component this individual consumes as well as the quantity of food component that is consumed.[3] There are a possible total of 45 foods and constituents that can be incorporated into the DII.[34] These variables include alcohol, carbohydrates, fiber, protein, spices and herbs, six categories of flavonoids, and various vitamins.[34] A full list is detailed in the DII development study.[34]

Data on foods and constituents consumed by participants is included in the NHANES dataset.[32] NHANES performed a dietary interview on participants of all ages by trained NHANES staff fluent in English and Spanish.[32] This interview was comprised of three sections: one in-person 24-hour dietary recall interview administered on the same day as the MEC examination, an interview on use of nutritional supplements and antacids on the same day as the MEC examination, and a second 24-hour dietary recall interview via telephone three to ten days after the MEC examination.[32] After the first dietary interview, participants were given objects and a booklet to aid them in reporting food quantities during the second interview over the phone.[32] Instruments for both 24-hour dietary recall interviews can be found on the NHANES website.[32] This study's calculation of DII scores used information from the first 24-hour dietary recall and included 25 of the 45 possible food components.

Study Population

Participant data was obtained from the National Health and Nutrition Examination Survey (NHANES) and is a combination of data collected from 2001 to 2006. NHANES is a national survey

meant to provide estimates of the health and nutritional status for the United States population. [35] It collected information in two-year cycles using a random-selection sampling design applied to multiple stages, considering counties, households, and individuals within households in order to create a nationally representative sample of the United States population. [32] Description of the staged recruitment process has been reported in detail elsewhere. [32]

Once the sampling design delineated target communities and households, the NHANES data collection crew sent notifications of arrival to those communities and letters to selected households introducing them to NHANES, indicating that they had been selected. [32] Once in the community, NHANES field interviewers went to each selected household and conducted a screener, which through an algorithm randomly selected individuals within those households to proceed to the MEC for further data collection. If selected, individuals would make an appointment for the MEC examination. NHANES outreach and examination materials were made available in English and Spanish. A small amount of money was given to participants in exchange for participation, ranging from $30 to $125 that depended on age and year of participation. A transportation allowance was also provided for those who drove to the MEC or a taxi was provided at no cost.[32]

The NHANES sample excluded institutionalized individuals, military personnel on active duty, and citizens living outside of the United States. [32] Final data were weighted to adjust for non-response and to ensure the final sample more closely mirrors the makeup of the population.[32]

The dataset used for this study was previously created by combining data from the 2001-2002, 2003-2004, and 2005-2006 year cycles. This combined NHANES dataset contains 31,509 cases. In this study, exclusions from the dataset included: those younger than 20 years of age; those with hs-CRP levels greater than 1.0 mg/dL, indicating acute inflammation; and individuals missing MetS component data, dietary information, or data from other covariates (age, sex, ethnicity, education, smoking, physical activity, BMI, hs-CRP, history of diabetes, history of coronary heart disease, history of cancer, and history of stroke). Due to these exclusions of all missing data, the final sample size of 4,076 remains

constant across all analyses, excluding analyses of subgroups, which are clearly noted. No other exclusion criteria were applied. See Figure 2 for details on sample sizes resulting from exclusions.

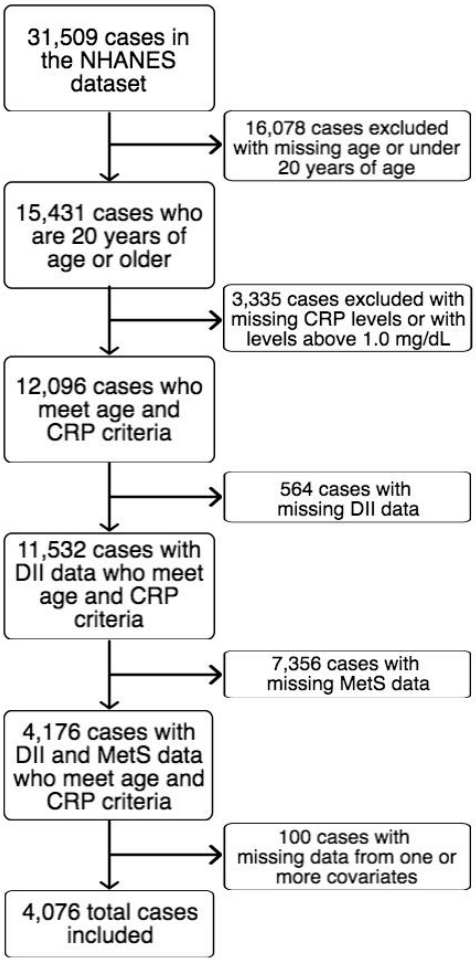

Figure 2. Flowchart of cases from the NHANES dataset included in the analysis.

Human Subjects

This study analyzed NHANES data, a national de-identified dataset. This qualifies this study for the human subjects exempt category that applies to existing data which are publically available and which cannot identify subjects.

Analysis of Data

Foods consumed by participants were converted into their constituent macro- and micro-nutrition components and subsequently into a dietary inflammatory index (DII) score. The DII score of each

participant served as the primary independent variable in this study and was treated as a continuous variable. MetS was used as the dependent variable. Each of the five components of MetS were categorized for each participant into "at-risk" or "not at-risk" for MetS according to thresholds set by the American Heart Association, the National Heart, Lung, and Blood Institute, the International Diabetes Federation Task Force on Epidemiology and Prevention, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity.[5] As stated, these five components included: sex-specific waist circumference, triglyceride levels, HDL cholesterol levels, blood pressure, and serum fasting glucose levels. If three or more of these components were considered at-risk for an individual, this individual was considered to have MetS. MetS was treated as a nominal variable with a "yes" or "no" dichotomous outcome.

Characteristics of NHANES participants were compared according to MetS grouping and DII values. Additional potential explanatory variables that were examined are as follows: sex (male, female), age (continuous), ethnicity (white, non-white), education level (less than 9^{th} grade, $9\text{-}11^{th}$ grade, high school grad, some college, college grad or above), history of diabetes (yes/borderline, no), history of heart attack (yes, no), history of stroke (yes, no), history of cancer (yes, no), history of coronary heart disease (yes, no), smoking status (current, non-current), physical activity (met ACSM, did not meet ACSM), BMI (continuous), and hs-CRP levels (continuous). Independent t-tests were used to determine if characteristics were different between the two MetS groups within continuous variables, and chi-square tests were used to determine if characteristics were different between the two MetS groups within categorical variables. Spearman correlation tests were used to assess significance of trends between continuous variables and DII. Independent t-tests were used to determine if DII scores significantly varied among dichotomous variables. Analysis of variance (ANOVA) tests were used to determine if DII scores significantly varied among categorical variables with three or more outcomes. Covariates with p values less than 0.10 in relation to both the primary independent variable (DII) and the dependent variable (MetS) were considered to be possible confounders and were incorporated into subsequent logistic

regression analyses. History of cancer, history of coronary heart disease, and history of heart attack did not meet these criteria and were not included in subsequent analyses.

Any necessary tests for associations between explanatory variables were conducted using Spearman's correlation test. History of diabetes and history of stroke were found to be significantly associated with one another. History of diabetes was chosen as a variable representative of these two correlated medical histories for subsequent analyses.

Analysis of MetS status according to the primary independent continuous DII variable were compared using three multiple binary logistic regression models. The fullest logistic regression model was also applied to each of the five components of MetS, with DII as the primary independent variable and MetS components dichotomized into "at-risk" and "normal" categories as the dependent variable. Stratifications were conducted for age (above mean/below mean), sex (male/female), history of diabetes (yes/no), hs-CRP levels (>0.3 mg/dL/ <=0.3 mg/dL), ethnicity (white/non-white), and BMI (>=30 kg/m^2/ <30 kg/m^2). For each of these variables, two datasets were created and the fullest logistic regression model, excluding the stratifying variable, was applied to both datasets. Logistic regression models were used to calculate odds ratios and 95% confidence intervals. All results were considered statistically significant if p values were less than 0.05. Analyses were performed using the SAS software (Version 9.4).

Results

NHANES Participant Characteristics

The final sample size consisted of 4,076 participants from the full NHANES 2001-2006 population sample. The study population had a mean age of 50.3, consisted of slightly more white participants (55%), and the majority had an education level of high school and above (71.1%). The sample was approximately evenly divided by sex. The mean BMI was 28 kg/m^2, the majority of individuals did not smoke (78.1%) and did not meet recommended amounts of physical activity (84.6%). The mean of hs-CRP levels was 0.27 mg/dL with 35.5% of individuals at elevated levels (greater than 0.3 mg/dL). A total of 3.56% of individuals had a history of stroke, 4.7% had a history of heart attack, 4.9%

had a history of coronary heart disease, 9.4% had a history of cancer, and 12.8% had a history of diabetes. Considering components of MetS, 41.4% of the population was hypertensive, 34.8% had at-risk HDL levels, 58.2% had a waist circumference considered to be at-risk, 39.6% had elevated triglyceride levels, and 42.4% had at-risk plasma glucose levels.

Baseline characteristics of sample participants broken down by MetS status are shown in Table 1. A total of 1743 individuals (42.8%) had MetS. Those with MetS were more likely to be older, white, and less physically active. They also had higher hs-CRP levels, were less likely to be a current smoker, had a higher BMI, and were less likely to have a history of heart attack, stroke, coronary heart disease (CHD), and diabetes when compared to the group without MetS. There was no significant difference in gender between the groups. The mean age among those with MetS was 58 years old while the mean age among those without MetS was 45 years old.

	Metabolic syndrome status		
	Present (n=1743)	**Not Present** (n=2333)	**p-value***
	n (%) or n [mean]		
Dietary inflammatory index	1743 [-0.1043]	2333 [-0.3261]	<0.0001
Age	1743 [57.39]	2333 [44.90]	<0.0001
Sex			0.7229
Female	857 (49.17)	1134 (48.61)	
Male	886 (50.83)	1199 (51.39)	
Education			<0.0001
Less than 9th grade	321 (18.42)	270 (11.57)	
9-11th grade	263 (15.09)	322 (13.80)	
High school grad	454 (26.05)	530 (22.72)	
Some college	431 (24.73)	698 (29.92)	
College grad or above	274 (15.72)	513 (21.99)	
Race/Ethnicity			<0.0001
Non-Hispanic Black	223 (12.79)	442 (18.95)	
Other Hispanic	50 (2.87)	75 (3.21)	
Mexican American	411 (23.58)	462 (19.80)	
Other race or multiracial	55 (3.16)	94 (4.03)	
Non-Hispanic White	1004 (57.60)	1260 (54.01)	
			0.0223
White	1004 (57.60)	1260 (54.01)	
Non White	739 (42.40)	1073 (45.99)	
Physical Activity			0.0002
Did not meet ACSM	1518 (87.09)	1932 (82.81)	
Met ACSM	225 (12.91)	401 (17.19)	

hs-CRP, continuous	1743 [0.3463]	2333 [0.2285]	<0.0001
hs-CRP, categorical			<0.0001
Normal (<= 0.3 mg/dL)	917 (52.61)	1711 (73.34)	
Elevated (0.3 mg/dL to 1.0mg/dL)	826 (47.39)	622 (26.66)	
Smoking status			0.0013
Not current	1404 (80.55)	1781 (76.34)	
Current	339 (19.45)	552 (23.66)	
BMI, continuous (kg/m^2)	1743 [31.3415]	2333 [26.2625]	<0.0001
HDL cholesterol (mg/dL)	1535 [44.0847]	2333 [57.3275]	<0.0001
Diastolic blood pressure (mm Hg)	1510 [73.1616]	2333 [69.0930]	<0.0001
Systolic blood pressure (mm Hg)	1510 [136.2]	2333 [119.2]	<0.0001
Triglycerides (mg/dL)	1450 [229.2]	2333 [113.7]	<0.0001
Waist Circumference (cm)	1735 [107.2]	2333 [91.9]	<0.0001
Glucose, plasma (mg/dL)	1450 [121.7]	2333 [95.6]	<0.0001
History of cancer			<0.0001
No	1540 (88.35)	2153 (92.28)	
Yes	203 (11.65)	180 (7.72)	
History of heart attack			<0.0001
No	1629 (93.46)	2254 (96.61)	
Yes	114 (6.54)	79 (3.39)	
History of stroke			<0.0001
No	1650 (94.66)	2281 (97.77)	
Yes	93 (5.34)	52 (2.23)	
History of coronary heart disease			<0.0001
No	1617 (92.77)	2259 (96.83)	
Yes	126 (7.23)	74 (3.17)	
History of diabetes			<0.0001
No	1340 (76.88)	2215 (94.94)	
Yes or borderline	403 (23.12)	118 (5.06)	

Table 1 Characteristics of NHANES participants (2001-2006) according to metabolic syndrome status. Exclusion of participants <20 years old and with CRP levels >=1.0mg/dL. *p-values are based on t-test for continuous variables and chi-square tests for categorical variables.

Baseline characteristics of sample participants in relation to DII score are shown in Table 2. The sample population had a mean DII score of -0.23 with an overall range in scores from -4.97 to 3.93 (standard deviation=1.55). Those who had the following characteristics were significantly correlated with DII score: older, female, non-white, less educated, less physically active, higher hs-CRP level, current smoker, higher BMI, higher systolic blood pressure, with a history of stroke, and with a history of diabetes. There was no statistically significant relationship between DII and HDL cholesterol levels,

diastolic blood pressure, triglyceride levels, waist circumference, plasma glucose levels, history of cancer, history of heart attack, and history of coronary heart disease.

Correlates of the Dietary Inflammatory Index (continuous)		
	Spearman's r statistic or n [mean]	**p-value****
Metabolic Syndrome		<0.0001
Present	1743 [-0.1043]	
Not present	2333 [-0.3261]	
Age	r=0.04851	0.0019
Gender		<0.0001
Female	1991 [0.0572]	
Male	2085 [-0.5067]	
Education Less than 9th grade (1); 9-11th grade (2); High school grad (3); Some college (4); College grad or above (5)	r=-0.20608	<0.0001
Race/Ethnicity		<0.0001
White	2264 [-0.3528]	
Non-White	1812 [-0.0794]	
Physical Activity		0.0003
Did not meet ACSM	3450 [-0.1917]	
Met ACSM	626 [-0.4490]	
hs-CRP, continuous	r=0.11308	<0.0001
hs-CRP, categorical		<0.0001
Normal (<= 0.3 mg/dL)	2628 [-0.3333]	
Elevated (0.3 mg/dL to 1.0 mg/dL)	1448 [-0.0460]	
Smoking status		0.0002
Not Current (0)	3185 [-0.2791]	
Current (1)	891 [-0.0601]	
Body mass index (kg/m^2)	r=0.03725	0.0174
HDL cholesterol (mg/dL)	r=-0.01249	0.4373
Diastolic blood pressure (mm Hg)	r=0.00558	0.7295
Systolic blood pressure (mm Hg)	r=0.06612	<0.0001
Triglycerides (mg/dL)	r=-0.00430	0.7916
Waist Circumference (cm)	r=0.00088	0.9552
Glucose, plasma (mg/dL)	r=0.02058	0.2056
History of cancer		0.4321
No	3693 [-0.2247]	
Yes	383 [-0.2939]	
History of heart attack		0.1606
No	3883 [-0.2393]	
Yes	193 [-0.0684]	
History of stroke		0.0014
No	3931 [-0.2465]	
Yes	145 [0.1815]	
History of coronary heart		0.7917

disease		
No	3876 [-0.2297]	
Yes	200 [-0.2615]	
History of diabetes		0.0030
No	3555 [-0.2587]	
Yes or borderline	521 [-0.0441]	

Table 2. Characteristics of NHANES participants (2001-2006) according to continuous dietary inflammatory index score. **p-values are based on Spearman's correlation tests with continuous variables, and independent t-tests for binomial variables.

Multivariate Logistic Regression Analyses

We examined the relationship between DII and MetS and considered the potential confounding roles of other covariates through three logistic regression models (see Table 3). All three models showed significant global likelihood ratio p values of <0.0001. Model 1 adjusted for sex and age and showed a significant odds ratio (OR) of 1.088 for DII, which indicated that individuals with higher DII scores were more likely to have MetS (95% CI=1.042-1.137; p=0.0001). Specifically, for every unit increase in the DII score, there is an estimated 8.8% increase in the likelihood of having MetS. Model 2 additionally adjusted for ethnicity, education level, history of diabetes, smoking status, and physical activity. Model 2 also showed a significant OR of 1.060 for DII, indicating that a higher DII score was associated with increased risk of MetS (95% CI=1.013-1.110; p=0.0122). Model 3 adjusted for all covariates in Model 2 and for BMI and hs-CRP levels. Incorporation of BMI and hs-CRP attenuated the significant contribution of DII to the likelihood of having MetS (OR=1.035; 95% CI=0.983-1.090; p=0.1921). In contrast, age (beta coefficient=0.0403;p<0.0001), ethnicity (beta coefficient=-0.2588; p=0.0024), education level (beta coefficient=-0.1328; p<0.0001), history of diabetes (beta coefficient= 1.0144; p<0.0001), smoking status (beta coefficient=0.2264; p=0.0213), BMI (beta coefficient=0.1951; p<0.0001), and hs-CRP levels (beta coefficient=0.9526; p<0.0001) were all associated with MetS status (see Table 4). Those with the following characteristics had significantly higher odds of having MetS: older, white, less educated, history of diabetes, currently smoking, less physically active, higher BMI, and higher hs-CRP levels (Table 4).

The relationship between DII as a continuous variable and a dichotomous hs-CRP outcome (normal/ elevated) was also examined through logistic regression modeling. The model adjusted for age,

sex, ethnicity, education level, history of diabetes, smoking status, physical activity, and BMI. This model showed a significant OR of 1.063 for DII, which indicated that individuals with higher DII scores were more likely to have elevated hs-CRP levels (95% CI=1.015-1.114; p=0.0098).

Full sample (n=4076)	**Global likelihood ratio p-value**	**Likelihood based R^2**	**DII Beta-Coefficient Estimate**	**DII Standard Error**	**DII P-value**	**DII Odds Ratio (95% CI)†**
Model 1*	<0.0001	0.1101	0.0847	0.0222	0.0001	1.088 (1.042-1.137)
Model 2**	<0.0001	0.1502	0.0584	0.0233	0.0122	1.060 (1.013- 1.110)
Model 3***	<0.0001	0.3078	0.0344	0.0263	0.1921	1.035 (0.983-1.090)

† Odds ratio interpreted as increase in odds of having MetS for every unit increase in DII score.
*Model 1: adjusted for sex and age
**Model 2: adjusted for Model 1 + ethnicity, education level, history of diabetes, smoking status, and physical activity.
***Model 3: adjusted for Model 2+ BMI and hs-CRP

Table 3 Associations between continuous DII and dichotomous MetS within NHANES (2001-2006) participants.

Variables	**Beta coefficient estimate**	**Standard error**	**P-value**
Dietary Inflammatory Index Score	0.0344	0.0263	0.1921
Sex	0.1046	0.0805	0.1935
Age	0.0403	0.00238	<0.0001
Ethnicity	-0.2588	0.0853	0.0024
Education level	-0.1328	0.0319	<0.0001
History of diabetes	1.0144	0.1275	<0.0001
Smoking status	0.2264	0.0983	0.0213
Physical activity	-0.1213	0.1080	0.2616
Body mass index	0.1951	0.00891	<0.0001
CRP levels	0.9526	0.1773	<0.0001
*model was adjusted for sex, age, ethnicity, education level, history of diabetes, smoking status, physical activity, BMI, and hs-CRP levels			

Table 4. Output of Model 3- logistic regression analysis between continuous DII as predictor variable and MetS as outcome variable, including 9 other explanatory variables, within NHANES (2001-2006).

Analysis of MetS Components

We examined the relationship between DII scores as a continuous independent variable and each of the five MetS components as dichotomous dependent variables: waist circumference, blood pressure, HDL cholesterol levels, triglycerides levels, and glucose levels. Each of the five dependent variables was dichotomized as at-risk or not at-risk based on the clinical cut-off points discussed earlier. Five separate

logistic regression models were run with the full list of covariates, equivalent to the Model 3 used with MetS as a dependent variable (Table 5). We found that DII significantly contributed to the likelihood of having at-risk blood pressure (OR=1.078; 95% CI=1.027-1.133; p=0.0026) and at-risk HDL levels (OR=1.090; 95% CI=1.039-1.143; p=0.0004). DII did not have a significant contribution to the likelihood of having an at-risk waist circumference, at-risk triglyceride levels, or at-risk plasma glucose levels.

	DII beta coefficient	**DII P-value**	**DII odds ratio (95% CI)**
Waist circumference	-0.0285	0.4645	0.972 (0.900-1.049)
Blood pressure	0.0755	0.0026	1.078 (1.027-1.133)
HDL cholesterol	0.0861	0.0004	1.090 (1.039-1.143)
Triglycerides	-0.0339	0.1588	0.967 (0.922-1.013)
Glucose	-0.00178	0.9454	0.998 (0.949-1.051)
Adjustments made: sex, age, ethnicity, education level, history of diabetes, smoking status, physical activity, BMI, and hs-CRP level			

Table 5. Adjusted odds ratios (95% confidence intervals) for the five metabolic syndrome components.

Stratification of Results

We examined the association between the DII and MetS with stratification by sex, age, ethnicity, diabetes, BMI, and hs-CRP levels. The effect of the DII on MetS did not significantly differ between those who: were white and non-white, did and did not have a history of diabetes, were obese and not obese, had normal and elevated hs-CRP levels. Stratifying results by sex showed that DII had a significant contribution to MetS among females but did not have a significant contribution to MetS among males (Table 6). Among females, every unit increase in one's DII score significantly increased the odds of having MetS by 8.0% (OR=1.080; 95% CI=1.002-1.163; p=0.0430). On average, this equates to twice the risk of having MetS for females with a DII score at the upper, most inflammatory bound as opposed to a DII score at the lower, least inflammatory bound.

	DII mean	**DII beta coefficient**	**DII p-value**	**DII odds ratio (95% CI)**
Females (n=1991)	0.0572	0.0765	0.0430	1.080 (1.002-1.163)
Males (n=2085)	-0.5067	0.0173	0.6456	1.017 (0.945-1.096)
Adjustments made: age, ethnicity, education level, history of diabetes, smoking status, physical activity, BMI, and hs-CRP level				

Table 6. Adjusted odds ratios (95% confidence intervals) for MetS, stratified by sex.

Stratifying results by age showed that DII had a significant contribution to MetS among individuals in the older group but did not have a significant contribution to MetS among individuals in the younger group (Table 7). Among older individuals, every unit increase in one's DII score significantly increased the odds of having MetS by 8.8% (OR=1.088; 95% CI=1.014-1.167; p=0.0184). On average, this means that older individuals with a DII score at the upper, most inflammatory bound are 2.14 times more likely to have MetS than those with a DII score at the lower, least inflammatory bound.

Age group	**DII mean**	**DII beta coefficient**	**DII p-value**	**DII odds ratio (95% CI)**
>=50.25* (n=1958)	-0.1786	0.0843	0.0184	1.088 (1.014-1.167)
<50.25 (n=2118)	-0.2799	0.00767	0.8431	1.008 (0.934-1.087)
Adjustments made: sex, ethnicity, education level, history of diabetes, smoking status, physical activity, BMI, and hs-CRP level **Mean age for the whole group (n=4076) was 50.25.				

Table 7. Adjusted odds ratios (95% confidence intervals) for MetS, stratified by age.

Further sub-stratification of results by sex and by age showed that DII had the strongest and most significant contribution to MetS among older females (Table 8). Among older females, every unit increase in one's DII score significantly increased the odds of having MetS by 10.4% (OR=1.104; 95% CI=1.002-1.216; p=0.0466). On average, this means that older females with a DII score at the upper, most inflammatory bound are 2.44 times more likely to have MetS than those with a DII score at the lower, least inflammatory bound. The strength of DII's predictive ability became weaker and non-significant among younger females as compared to all females (OR=1.064; 95% CI=0.950-1.192; p=0.2816). The strength of DII's predictive ability became stronger and more significant among older males as compared to all males (OR=1.085; 95% CI=0.980-1.201; p=0.1170).

	DII mean	DII beta coefficient	DII p-value	DII odds ratio (95% CI)
Females >=50.25 years old (n=974)	0.0515	0.0987	0.0466	1.104 (1.002-1.216)
Females <50.25 years old (n=1017)	0.0627	0.0622	0.2816	1.064 (0.950-1.192)
Males >=50.25 years old (n=984)	-0.4064	0.0814	0.1170	1.085 (0.980-1.201)
Males <50.25 years old (n=1101)	-0.5963	-0.0414	0.4471	0.959 (0.862-1.068)
Adjustments made: ethnicity, education level, history of diabetes, smoking status, physical activity, BMI, and hs-CRP level				

Table 8. Adjusted odds ratios (95% confidence intervals) for MetS, stratified by sex and by age.

Discussion

In this study, we compared the effect of inflammatory properties of one's diet, as measured by the DII, in relation to MetS status in the nationally representative NHANES dataset. DII scores were found to be significantly and positively associated with MetS among individuals above the age of 50 after adjusting for other covariates related to socio-economic and behavioral factors. DII scores were also found to be significantly and positively associated with MetS among females, although the reasoning behind this association is not fully understood and should be interpreted with caution. DII scores were found to be significantly and positively associated with hypertension and high HDL cholesterol levels, two components of MetS. DII scores were not found to be significantly associated with the remaining components of MetS: waist circumference, triglyceride levels, and glucose levels. These three components remained non-significant when data was stratified by age and by sex. Higher DII scores were found to significantly predict elevated hs-CRP levels after adjusting for covariates related to socioeconomic and behavioral factors.

Three logistic regression models with an accumulating combination of covariates were used to assess the possible role of confounders in the relationship between DII and MetS. Major demographic and socio-economic characteristics were considered as explanatory variables in these models: age, sex, ethnicity, and education level. Other behaviorally-related variables were also considered that could affect health outcomes and may subsequently confound dietary effects, inflammation, or MetS status: BMI, smoking status, physical activity level, hs-CRP levels, history of coronary heart disease, history of stroke,

history of heart attack, and history of cancer. Since MetS has been linked to the development of diabetes or cardiovascular diseases, history of these diseases were considered. [1] Major risk factors for MetS are age and physical inactivity, which made these two variables confounders to consider. [4] Waist circumference is a component of MetS in part because it is indicative of the relationship between upper-body fat and insulin resistance. [4] BMI was included as a covariate due to its close resemblance to waist circumference and because it has been shown to be positively associated with the production of inflammatory cytokines.[4] Smoking status is considered to be a key risk factor for the development of cardiovascular disease and for this reason was also considered as a covariate in these analyses.[4] Each of these covariates was statistically examined in relation to both DII and MetS (Tables 1 and 2). All covariates that were significantly related to both the primary independent variable and the dependent variable were included in logistic regression modeling, with the exception of sex which was not found to be significantly related to MetS but was nonetheless included.

Logistic regression analyses were conducted looking at the relationship between DII and hs-CRP and hs-CRP and MetS. It was found that hs-CRP is significantly and positively associated with DII, which is consistent with findings from other studies conducted, including validation studies. [3,14,27] It was found the hs-CRP is also significantly and positively associated with MetS outcome (Table 4), which is consistent with findings from other studies.[8-10]

Model 1 only incorporated the two most basic demographic characteristics: sex and age. After these were incorporated, the relationship between DII and MetS was statistically significant and indicative of positive MetS status with increasing DII scores. Model two incorporated socio-economic factors and most behavioral factors: ethnicity, education level, history of diabetes, smoking status, and physical activity. The relationship between DII and MetS was still statistically significant after these factors were incorporated (Table 3). After Model 3's covariates (BMI and hs-CRP) were incorporated, however, the significant relationship between DII and MetS was found to be weaker and no longer significant. These analyses were conducted on the full sample of 4,076 participants.

When looking at these same models but stratified by age, the relationship between DII and MetS significantly changed. When looking at a group of individuals below the mean age of 50, the DII never had a significant relationship with MetS, even before any covariates were factored into the modeling. On the other hand among a group of individuals above the mean age of 50, the relationship between DII and MetS remained significant after all covariates were incorporated into logistic regression analyses. Age is a known condition that is associated with the development of MetS.[4] This, however, does not explain the relationship between a diet's inflammatory properties and age. It was found in this study population that one's DII score was significantly positively associated with an increase in age (Spearman's r=0.04851; p=0.0019). It is possible that an older age allowed for more time for a diet's inflammatory properties to take effect on one's body. It is also possible that a higher prevalence of MetS for older individuals increased the power to find an association among those groups. MetS prevalence was much higher in the older age group (58.6%) than the younger age group (28.1%). These findings are somewhat consistent with findings from other studies looking at the association between DII and MetS. Two studies did not find an association and both of these studies looked populations that varied from a lower age range close to 20 up until a higher age range close to 70.[27,28] One study did find a significant association between DII and MetS and this study excluded individuals below the age of 35, however this study also excluded those above the age of 60.[29] It would be interesting to further examine associations between DII and MetS stratified by 10-year age groups.

When looking at these models stratified by sex, the relationship between DII and MetS was also significantly affected. In males, the relationship between DII and MetS was significant when no covariates were incorporated, but immediately became non-significant in Model 1 once age was incorporated. Among females, the relationship between DII and MetS remained significant after all covariates were incorporated into analyses. There was a similar prevalence of MetS in both groups (42.5% in males and 43.0% in females). Differences in BMI and hs-CRP distributions among males and females were examined. While BMI levels were very similar, it was found that elevated hs-CRP levels were much more prevalent in females than in males (43.2% in females; 28.2% in males). Still when sex

groups were further stratified by hs-CRP levels, the stratified groups both retained similar ORs to the overall sex group within both males and females, and the associations became non-significant in both hs-CRP groups for females most likely due to loss of power from smaller sample sizes. When sex groups were further stratified by age, it was found that the OR for DII was strongest and statistically significant in older females. The impact of DII on MetS was stronger and more significant in older men than it was in younger females, which leads us to hypothesize that age is a stronger factor of influence on DII's predictive ability of MetS than sex (Table 8). It is not fully understood why the association between DII and MetS is stronger among females as opposed to males. Gender differences in the effectiveness of diagnostic criteria to identify individuals with MetS, as well as differences in glucose and lipid metabolism could potentially be contributing factors behind these findings. [36] To our knowledge, this stratification has been examined in one other previous study and it was found that females with DII scores in the highest quartile had reduced risk of MetS. [30] It would be interesting to further examine the interactions between DII and MetS according to sex groups.

The five separate MetS components were each analyzed in relation to DII. Having at-risk high blood pressure levels and at-risk low HDL levels were each found to be significantly predicted by higher DII scores. Having an at-risk high waist circumference, at-risk high triglyceride levels, and at-risk high plasma glucose levels were each found to be non-significantly predicted by DII scores. These three components remained non-significantly associated when stratified by sex and when stratified into two age groups around the mean. High blood pressure levels were significantly associated with higher DII scores in one other study.[29] Low HDL levels were significantly associated with higher DII scores in two other studies. [28,29] To our knowledge, high plasma glucose levels have only been significantly predicted by higher DII scores in one study, and high triglyceride levels have only been significantly predicted by higher DII scores in one study.[27,29]

Limitations and Strengths

There are several limitations to this study. Since this study is cross-sectional, it only examined an association between dietary habits and disease outcome. Therefore, it is not possible to determine if there

is causality in the association. It is not possible to determine if dietary habits or medication were altered as a result of health problems. All dietary data collected is self-reported. Since the 24-hour dietary recall only assessed one day of dietary habits, there is the possibility that dietary data is not entirely representative of an individual's average dietary habits. This would introduce non-systematic bias into the study and would skew results toward the null. It is believed by the DII's creators that the DII assesses diets as a whole, but could yield weaker associations because the tool was created looking at articles that examined relationships between single foods or dietary constituents and inflammatory levels, as opposed to dietary patterns.[3] Despite adjustments for many covariates, it is still possible that variables unaccounted for may have contributed to the significant findings. For example, other factors in the diets consumed that are associated with both the DII score and MetS may have confounded the association. The data collected for 2001-2006 NHANES studies was missing some information that would have been helpful to incorporate into this study. Only 25 of the total 45 DII components were available. However, many of the nutrient items not included in the final DII scores calculated from the NHANES dataset tend to be consumed in low quantities (e.g. turmeric). Given the role of inflammation in the relationship between DII and MetS, information on anti-inflammatory medication, such as aspirin, would have helped to incorporate this variable as a confounder in the analysis. The clinical definition for MetS included measures of the five components as well as guidelines as to whether certain drugs were taken by an individual. Information about intake of these drugs was missing from the NHANES dataset. The descriptive percentages of the sample population with given characteristics have not been weighted, so they cannot be assumed to be representative of the United States population. These percentages will be weighted in a manuscript submission.

There are various strengths to this study that were offered through the use of the NHANES dataset. The sample used was large and population based. All data collection was reliable and valid, and it can be assumed that all measurements made were accurate. The presence of many variables in the dataset allowed for many confounders to be factored into analyses. Another strength is the use of the DII, which is a validated tool that was developed in relation to biological outcome measures.

Conclusion

Metabolic syndrome currently affects one third of adults in the U.S. and has been associated with a variety of chronic diseases that pose a burden to the nation. [1,2] In the nationally representative NHANES dataset (2001-2006), dietary inflammatory index scores were found to significantly predict metabolic syndrome outcome among individuals above the age of 50 (OR=1.088; 95% CI=1.014-1.167; p=0.0184). Individuals older than 50 years of age who consume diets very high inflammatory properties were found to be 2.14 times more likely to have metabolic syndrome than those who consume a diet with very low inflammatory properties. This study supports the hypothesis that there is a link between diet and metabolic syndrome, possibly through inflammatory mechanisms. Future research to establish causality between the dietary inflammatory index and metabolic syndrome could lead to further developments in the utilization of the DII as a tool for dietary intervention of this syndrome.

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