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Dietary inflammatory potential and risk of mortality in metabolically healthy and unhealthy phenotypes among overweight and obese U.S. adults

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Abstract

Background and Aims—This study was designed to investigate the association between the dietary inflammatory index (DII®) scores, metabolic phenotypes, and risk of mortality risk in overweight/obese individuals from a representative sample of the U.S. population.

Methods—Data from 3733 overweight/obese adults (BMI≥25kg/m^2) aged 20–90 years from the National Health and Nutrition Examination Survey III, 1988–1994 were analyzed; these participants were followed for mortality through December 31, 2011. DII scores were computed based on baseline dietary intake using 24-hour dietary recalls. Metabolically unhealthy status was

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STATEMENT OF AUTHORSHIP

YMP and SSL: project conception, development of overall research plan; YMP and KH: statistical analyses; YMP and MKC: writing of the manuscript; YMP, MKC, SSL, NS, KH, SES, JRH, ATM, DPS: interpretation of the data and critical revision of the manuscript for important intellectual content. YMP and SSL: had primary responsibility for final content. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII)™ from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. Otherwise, none of the authors reported a conflict of interest related to the study.

defined as having 2 or more of these metabolic abnormalities: high glucose, insulin resistance, elevated blood pressure, triglycerides, C-reactive protein levels, or low high-density lipoprotein-cholesterol values.

Results—In metabolically unhealthy overweight/obese (MUO) individuals, DII score was associated with increased risk of all-cause mortality ($HR_{Tertile\ 3\ vs\ Tertile\ 1}$ 1.44; 95% CI 1.11–1.86 P_{trend}=0.008; $HR_{1SD\ increase}$ 1.08; 95% CI 0.99–1.18). Additionally, a stronger association with cardiovascular mortality was observed ($HR_{T3\ vs\ T1}$ 3.29; 95% CI 2.01–5.37 P_{trend}<0.001; $HR_{1SD\ increase}$ 1.40; 95% CI 1.18–1.66), after adjusting for potential confounders. Furthermore, when analyses were restricted to obese individuals (BMI≥30 kg/m^2), the association was more pronounced, especially for cardiovascular mortality ($HR_{T3\ vs\ T1}$ 5.55; 95% CI 2.11–14.57 P_{trend}=0.006; $HR_{1SD\ increase}$ 1.74; 95% CI 1.21–2.50). No association was observed between DII score and risk of mortality in individuals with metabolically healthy overweight/obese (MHO) phenotype, or for cancer mortality in either MHO or MUO phenotype.

Conclusions—A pro-inflammatory diet appears to increase risk of all-cause and cardiovascular mortality in the MUO phenotype, but not among the MHO phenotype.

Keywords

National Health and Nutrition Examination Survey III; Dietary Inflammatory Index; overweight; obesity; metabolic health; mortality

INTRODUCTION

Chronic low-grade inflammation is commonly described in chronic conditions such as obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) (1). It has been suggested that various food components and dietary patterns modulate chronic inflammation (2). The Dietary Inflammatory Index (DII®) was developed as a standardized scoring system to assess the influence of diet on inflammation (3). High DII score has been positively associated with increased levels of inflammatory markers including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 and tumor necrosis factor α receptor 2 (4), as well as higher risk of CVD (5) and mortality (6).

In obese individuals, overburdened adipose tissues secrete inflammatory proteins, such as leptin and TNFα, contributing to insulin resistance (7) and increased risk of CVD (8). However, some studies have reported a subset of obese individuals who are protected from these harmful effects (9). This subset, categorized as the metabolically healthy obese (MHO) phenotype, demonstrates lower insulin resistance and favorable metabolic profiles, compared to their counterparts with similar BMI, but with other metabolic abnormalities commonly referred to as the metabolically unhealthy obese (MUO) phenotype. The MHO phenotype demonstrates lower risk of CVD (10), cancer (11), and all-cause mortality (12) compared to the MUO phenotype. The role of genetic predisposition and lifestyle factors has been suggested to explain the MHO phenotype (13).

Patterns of dietary intake may play a role in determining risk within MHO and MUO phenotypes (14–16). However, several studies have reported inconsistent results (14, 17–20), and various limitations have been proposed (21). In addition, the differential effect of dietary

intervention in MHO and MUO phenotype has been investigated in several studies (22–26). These studies have reported some differences in the biologic responses between MHO and MUO phenotypes, ranging from differences in the magnitude of insulin sensitivity improvement (22) to certain metabolic parameters that improved only in the MUO phenotype (23–25). While these studies have focused on relatively short-term outcomes, such as changes in insulin sensitivity, lipid profile or fat mass, our previous study assessing mortality, showed that a healthy Mediterranean diet is associated with decreased mortality risk only in the MHO phenotype (21). However, it is unclear how pro-inflammatory diet would differentially affect the natural history of inflammation-related conditions in MHO and MUO individuals.

Here we use data from a prospective study of a nationally representative U.S. population to test the hypothesis that pro-inflammatory diet will show differential association with mortality risk in MHO and MUO phenotypes.

MATERIALS AND METHODS

Study population

Data from individuals participating in the National Health and Nutrition Examination Survey (NHANES) III from 1988–1994 and followed up for death through December 31, 2011 were used. The NHANES III was carried out using a complex, multi-stage, stratified, clustered, probability sampling design to obtain a nationally representative sample of the civilian, non-institutionalized US population.

We analyzed data from 5256 overweight ($25 \leq BMI < 30$ kg/m^2) or obese (BMI ≥ 30kg/m^2) adults aged 20–90 years at baseline based on measured height and weight, who had complete data on mortality follow-up, a single 24-hour dietary recall (24HR) and cardio-metabolic parameters including blood pressure (BP), fasting glucose, insulin, triglycerides, high-density lipoprotein cholesterol (HDL-C), and hs-CRP. Individuals with a history of stroke (n= 130), myocardial infarction (n= 235), congestive heart failure (n= 160), or cancer (other than skin cancer) (n= 196) were excluded. To reduce the possibility of misclassification, we excluded individuals who reported modifying their dietary intake in the previous 1 year due to any medical reason or general health concern (n= 990). Individuals who reported implausible values of energy intakes (<500 and >5 000 kcals/d) (n= 89), BMI > 50 kg/m^2 (n= 17) or were pregnant or lactating (n= 25) also were excluded. Finally, we analyzed data from a total of 3733 individuals.

Assessment of dietary inflammatory index

Dietary intake was evaluated using the 24HR data that were validated by the Nutrition Methodology Working Group (27). A single 24HR was used to calculate the DII score. The development of the DII is reported in detail by Shivappa *et al.* elsewhere (3). Briefly, a total of 1943 articles were reviewed and scored. Forty-five food parameters, including nutrients, foods, and bioactive compounds, were evaluated based on their inflammatory effect on six specific inflammatory markers, including C-reactive protein (CRP), IL-1β, IL-4, IL-6, IL-10 and tumor necrosis factor (TNF)-α. A database constructed from 11 countries and

representing global daily intake for each of the 45 parameters was used as standard dietary intake to calculate the DII. A standard mean for each parameter from the world database was subtracted from the actual individual intake and divided by its standard deviation to generate Z scores. These Z scores were converted to proportions (with values from 0 to 1) to minimize effects of outliers in skewing the data. To achieve a symmetrical distribution with values center on ≈0, each proportion was doubled and then 1 was subtracted. Each centered proportion was then multiplied by the corresponding inflammatory effect score for each food parameter and summed across all food parameters, to yield the overall DII score. The DII consists of 45 food parameters which includes macro and micronutrients, flavonoids, spices and food items, each labeled with an inflammatory effect score (3).

In previous work, hs- CRP was used to investigate construct validity of the DII in a longitudinal cohort using multiple 7-day dietary recalls and 24HRs (28). Subsequently, the DII also was construct-validated among different populations with an extended array of inflammatory biomarkers (e.g., interleukin, IL-6, hs-CRP, and TNF-α) (4, 28, 29).

For the present study, 27 of the 45 food parameters were available for DII calculation: energy, carbohydrate, protein, fat, fiber, cholesterol, saturated fatty acid, mono-unsaturated fatty acid, poly-unsaturated fatty acid, niacin, thiamin, riboflavin, vitamin B6, vitamin B12, magnesium, zinc, selenium, iron, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, omega 3, omega 6 and alcohol. In previous validation work in the SEASONS Study, there was no decrease in predictive ability using only 28 of 45 parameters (28).

Assessment of metabolic health

Metabolic health was evaluated with metabolic parameters measured in accordance to the quality control standards of the Centers for Disease Control and Prevention. Body weight and height were measured to the nearest 0.01kg and 0.1cm; BMI was calculated as kg/m^2. An average value from five separate BP measurements was used in analyses. Serum glucose levels were measured with a modified hexokinase enzymatic method. Serum insulin levels were measured with radioimmnuoassay (Pharmacia Diagnostics, Uppsala, Sweden). Triglycerides and HDL-C levels were measured using a Hitachi 704 analyzer (Boehringer-Mannheim Diagnostics, Germany). Latex-enhanced nephlometry (Department of Laboratory Medicine, Immunology Division, University of Washington, Seattle, WA, USA) was used to measure serum hs-CRP concentrations. The coefficient of variation (CV) for each biochemical variable was: <4% for glucose, <14% for insulin, <6% for HDL-C, <6% for triglyceride, and <17% for hs-CRP (30). Because many NHANES III participants did not fully adhere to fasting instruction, we used data from individuals who had fasted for at least six hours in order to increase sample size (21).

We defined a participant as being metabolically unhealthy if he or she had 2 or more cardio-metabolic abnormalities (fasting glucose ≥ 100 mg/dL or antidiabetic medication use, homoeostasis model assessment of insulin resistance [HOMA-IR = fasting glucose (mg/dl) × fasting insulin (IU/mL)/405] greater than the 90^{th} percentile, systolic/diastolic BP ≥ 130/85 mm Hg or antihypertensive medication use, triglycerides ≥ 150 mg/L or cholesterol-lowering medication use, HDL-C < 40 mg/dL in men or < 50 mg/dL in women or cholesterol-lowering medication use, and hs-CRP greater than the 90^{th} percentile) (9).

Assessment of Mortality

To identify the vital status and cause of death, the National Center for Health Statistics linked all participants to the National Death Index through December 31, 2011. Each participant was followed from the date of the examination to December 31, 2011 or the date of death. The underlying cause found on the death certificate was employed to identify cause of death, based on the underlying Cause of Death-113 groups (International Classification of Disease (ICD), Tenth revision). All-cause mortality was defined as deaths from any underlying cause of death; CVD and cancer mortality was defined as deaths due to cause of death codes ICD-10 I00-I69 and C00-C97, respectively (31).

Statistical Analysis

All statistical analyses were conducted using SAS® software, version 9.3 (SAS Institute Inc., Cary, NC, USA). We used the appropriate survey procedures to account for the complex sampling design and weights. Descriptive results were presented as unweighted counts (n) and weighted percentages. For the subgroup analysis, domain analysis was applied to preserve the complex sampling in which the entire sample was used to estimate the variance of subpopulations. Continuous variables were expressed as mean ± SE (SE: standard error) and compared with linear regression analyses. Categorical variables were expressed as percentages with SE and were analyzed using Rao-Scott chi-squared tests. P value less then . 05 was considered statistically significant.

We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, CVD, and cancer mortality. The proportional hazards assumptions were evaluated by the logarithm of cumulative hazards function based on Kaplan-Meier estimates for DII tertile group as well as categorical age, sex, and race/ethnicity. Potential covariates were identified *a priori* based on literature review. The following covariates were included in multivariable-adjusted models: age at baseline, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, or others), educational attainment (<12 years, 12 years, or >12 years of education), income (low [poverty income ratio (PIR) ≤ 1.3], middle [1.3<PIR ≤ 3.5], and high [PIR>3.5]), smoking status (never, former, and current) and level of physical activity (inactive, insufficient activity, recommended activity). Recommended physical activity was defined as self-reported leisure-time moderate activity (3≤ metabolic equivalents (METs) <6) five or more times per week or leisure time vigorous activity (METs ≥6) 3 or more times per week; physically inactive was defined as no reported leisure-time physical activity; and insufficient physical activity as not meeting the criteria for recommended levels of physical activity but not inactive (32).

We estimated age-, sex-, and race/ethnicity–adjusted HRs (model 1) as well as age-, sex-, race/ethnicity and BMI-adjusted HRs (model 2). In the final model, we further adjusted for education, income, smoking status, and level of physical activity. Missing values for income were substituted as a dummy variable. The potential effect modification of DII by age group, sex, race/ethnicity, smoking, adherence to recommended physical activity, and obesity was assessed through the stratified analysis and interaction tests. The interaction testing was conducted using all-cause and cardiovascular mortality as the outcome by including the cross-product interaction terms in the Cox proportional hazards models based on

Satterthwaite adjusted F test. In addition, several sensitivity analyses were carried out: (i) using metabolic syndrome as an alternative definition of metabolic health, defined as an individual with ≤3 cardio-metabolic abnormalities (fasting glucose ≥ 100 mg/dL or antidiabetic medication use, systolic/diastolic BP ≥ 130/85 mm Hg or antihypertensive medication use, triglycerides ≥ 150 mg/L or cholesterol-lowering medication use, HDL-C < 40 mg/dL in men or < 50 mg/dL in women or cholesterol-lowering medication use, and waist circumference ≥102 cm in men or ≥88 cm in women) (33), (ii) re-analysis after excluding individuals who died during the first five years of follow-up, and (iii) exploring association only for obese (BMI ≥ 30) individuals.

RESULTS

The MUO phenotype (n=1918) was found in 50.3% (SE 1.8 %) of those who were overweight or obese. In MUO individuals, those in the highest DII tertile were less likely to be men and non-Hispanic White; were more likely to have lower education, lower income, lower proportion of moderate drinkers, and higher proportion of diabetes. With increasing DII in MUO individuals, BMI and hs-CRP tended to increase; and DBP tended to decrease. In MHO individuals, (n= 1815) those within the highest DII tertile were less likely to be men and non-Hispanic White; were more likely to have a lower education, lower income, and lower proportion of recommended physical activity. With increasing DII in MHO individuals, BMI, HOMA-IR, hs-CRP, and HDL-C tended to increase; and triglycerides tended to decrease. Individuals with the MUO phenotype were more likely to be male, non-Hispanic Whites, and ever-smokers compared to those with the MHO phenotype (Table 1 and Supplemental Table S1).

During a median follow-up of 18.5 years, there were 868 deaths (246 deaths for MHO and 622 deaths for MUO individuals). Multivariable-adjusted HRs and 95% CIs for all-cause, cardiovascular, and cancer mortality according to the tertile categories and a 1-SD increase in DII score are shown in Table 2 and Supplemental Table S2. In the population including both MHO and MUO individuals, the HRs for individuals in the second and the highest tertiles compared to those in the first tertile, respectively, were 2.02 (95% CI 1.50–2.71) and 2.50 (95% CI 1.60–3.91) (P_{trend} <0.001) for CVD mortality, after multivariable adjustment. A 1 SD increase in the DII score was also positively associated with risk of CVD mortality (HR 1.32; 95% CI 1.10–1.58). However, there was no association between DII and all-cause or cancer mortality.

HRs for all-cause, CVD and cancer mortality by tertile categories and a 1 SD increment in DII score in MHO and MUO individuals are shown in Table 3 and Supplemental Table S3. In MUO individuals, HRs in tertile 2 and tertile 3 were 1.41 (95% CI 1.15–1.73) and 1.44 (95% CI 1.11–1.86) (P_{trend} = 0.008) for all-cause mortality, and 2.48 (95% CI 1.79–3.44) and 3.29 (95% CI 2.01–5.37) (P_{trend} = <0.001) for CVD mortality, respectively, compared with those in tertile 1. A 1 SD increase in the DII was also positively associated with risk of all-cause and CVD mortality (HR 1.08; 95% CI 0.99–1.18 and HR 1.40; 95% CI 1.18–1.66, respectively). However, no increase of all-cause and CVD mortality was observed with increasing DII score among those with MHO phenotype, and there was no association between DII and cancer mortality in either MHO or MUO phenotype.

In stratified analyses for CVD mortality with a 1 SD increase in DII score, stronger positive associations were found in those <65 years and in obese individuals (P for interaction = 0.04 and 0.03, respectively) (Table 4). When we restricted the analysis to obese individuals, the strength of associations between DII and CVD mortality in MUO individuals were enhanced (Supplementary Table S4). Compared with tertile 1, HRs in tertile 2 and tertile 3, respectively, were 2.74 (95% CI 1.33–5.63) and 5.55 (95% CI 2.11–14.57) (P_{trend} = 0.008). A 1 SD increase in the DII was also positively associated with risk of CVD mortality (HR 1.74; 95% CI 1.21–2.50). Similar results were observed when metabolic syndrome was used as an alternative definition of metabolic health, demonstrating increased all-cause and CVD mortality exclusively in MUO phenotype and not in MHO phenotype (Supplementary Table S5). In addition, overall results did not materially change when individuals who died in the first 5 years of follow-up were excluded (Supplementary Table S6).

DISCUSSION

In this nationally representative study of US adults, higher DII score was associated with an increased risk of all-cause mortality and CVD mortality in the MUO phenotype, independent of potential confounders. The association between higher DII score and increased mortality was not observed in the MHO phenotype. This differential association of DII score with mortality risk in MHO and MUO phenotypes persisted in sensitivity analyses. To the best of our knowledge, the present study is the first to evaluate the differential association of pro-inflammatory diets with risk of mortality in MHO and MUO phenotypes.

Our results showing positive associations between high DII score and all-cause and CVD mortality among MUO phenotype is largely in accordance with the previously reported additive effect of inflammation on CVD risk among metabolically unhealthy individuals (34). Although the exact mechanism of how pro-inflammatory diet influences the host immune system is not fully understood, the possible mechanisms include skewing of the redox balance (35), saturated fatty acids triggering endoplasmic reticulum-stress responses (36) and increased levels of CRP and IL-6 (4). These mechanisms may share common features with the obesity-related pathophysiology observed in MUO phenotype, such as reactive oxygen species production by mitochondria (37) and increased levels of CRP and IL-6 (1). This overlap in mechanistic pathways may have a role in the association of pro-inflammatory diet with increased risk of mortality in MUO phenotype. In addition, our results generally support those of Fang et al. who reported a positive association between high DII score and all-cause, CVD and cancer mortality among US prediabetic adults, representing metabolically challenged populations (38).

Of note is that the positive association between high DII score and mortality was observed only in the MUO phenotype, suggesting that pro-inflammatory diets may aggravate the mortality risk exclusively in overweight/obese individuals with metabolic abnormalities. To date, several dietary intervention studies have separately assessed effects in MHO and MUO phenotypes (22–26, 39), with some studies reporting differential effects by phenotype (22–25). Similarly, in our previous study, we observed differential benefit in mortality reduction associated with Mediterranean diet between MHO and MUO phenotype (21). Furthermore, adherence to a high quality diet defined by Dietary Approaches to Stop Hypertension-style

prescription and the Healthy Eating Index was associated with decreased mortality only in the metabolically obese normal-weight phenotype, and not in metabolically healthy normal-weight phenotype (40). These results collectively suggest that certain dietary patterns may have differential effects according to the baseline metabolic phenotype (41). This, possibly synergistic, relationship between diet and metabolic phenotype may underscore the need for dietary interventions specified for each metabolic phenotype.

The association between high DII scores and CVD mortality was more pronounced than that observed for all-cause mortality. Previously, we showed that high DII score is positively associated with increased levels of CRP (4, 28) and homocysteine (42), both of which are known to be risk factors for CVD mortality (43, 44). In addition, several prospective studies consistently reported increased myocardial infarction (45) and CVD risk (5) in individuals consuming pro-inflammatory diet.

In subgroup analysis, associations between DII and CVD mortality in MUO individuals were stronger in adults <65 years of age, suggesting the potential need for early dietary intervention in this age group. Effects also were stronger among metabolically unhealthy obese individuals (BMI ≥ 30). This may be due to the greater amount of excess adiposity in obese individuals compared to overweight individuals, causing them to be more susceptible to the harmful effects of pro-inflammatory diet. On the basis of these findings, intensive weight loss programs that also incorporate an anti-inflammatory diet intervention may be beneficial in reducing risk of CVD mortality in MUO phenotype among obese individuals.

Strengths of our study include a long follow-up period of nearly 18 years and a prospective study design carried out in a representative sample of US population. Data were collected using standardized protocols to minimize measurement errors. Limitations of our study include dietary data being extracted from a single, self-reported 24HR, which is accompanied by relatively large intra-person variability and is therefore subject to misclassification in categorizing DII tertiles. A single 24HR was used to calculate DII scores in the present study because the NHANES III food frequency questionnaire was not designed to estimate nutrient intake. In addition, due to the single measurement of dietary intake, changes in dietary habits over time could not be integrated into the analysis. Furthermore, only 27 food parameters were available for DII calculation, out of a possible 45 food parameters. However, it has been shown that there is virtually no drop-off in predictive ability of the DII in calculations using <30 parameters (28). We also were unable to study the association between DII scores and the incidence of non-fatal CVDs or cancers because data were not available in NHANES III. Lastly, as in any observational study, residual or unmeasured confounding cannot be ruled out.

Our results suggest that increased consumption of pro-inflammatory diet, represented by high DII score, is associated with increased all-cause and CVD mortality exclusively in the MUO phenotype. As the primary goal of obesity management is to reduce morbidity and mortality from obesity-induced chronic inflammation, it is important to understand the differential association of pro-inflammatory diet with mortality in distinct metabolic phenotypes. The heightened risk of mortality among MUO phenotype, especially in young

to middle age, and in obese individuals, may warrant prioritization to obesity management including anti-inflammatory diet interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

DII	Dietary Inflammatory Index
CVD	cardiovascular disease
MHO	Metabolically Healthy Overweight/Obese
MUO	Metabolically Unhealthy Overweight/Obese
NHANES	National Health and Nutrition Examination Survey
HDL-C	high-density lipoprotein cholesterol

References

1. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444(7121):860–7. [PubMed: 17167474]
2. Park YM, Zhang J, Steck SE, Fung TT, Hazlett LJ, Han K, et al. Obesity Mediates the Association between Mediterranean Diet Consumption and Insulin Resistance and Inflammation in US Adults. The Journal of nutrition. 2017; 147(4):563–71. [PubMed: 28298537]
3. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public health nutrition. 2014; 17(8):1689–96. [PubMed: 23941862]
4. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. Annals of epidemiology. 2015; 25(6):398–405. [PubMed: 25900255]
5. Ramallal R, Toledo E, Martinez-Gonzalez MA, Hernandez-Hernandez A, Garcia-Arellano A, Shivappa N, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the SUN Cohort. PloS one. 2015; 10(9):e0135221. [PubMed: 26340022]
6. Shivappa N, Steck SE, Hussey JR, Ma Y, Hebert JR. Inflammatory potential of diet and all-cause, cardiovascular, and cancer mortality in National Health and Nutrition Examination Survey III Study. Eur J Nutr. 2017; 56(2):683–92. [PubMed: 26644215]
7. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993; 259(5091):87–91. [PubMed: 7678183]
8. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006; 444(7121):875–80. [PubMed: 17167476]

9. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med. 2008; 168(15):1617–24. [PubMed: 18695075]
10. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: A systematic review and meta-analysis. European journal of preventive cardiology. 2016; 23(9):956–66. [PubMed: 26701871]
11. Park YM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. International journal of cancer. 2017; 140(12):2657–66. [PubMed: 28268252]
12. Yang HK, Han K, Kwon HS, Park YM, Cho JH, Yoon KH, et al. Obesity, metabolic health, and mortality in adults: a nationwide population-based study in Korea. Scientific reports. 2016; 6:30329. [PubMed: 27445194]
13. Navarro E, Funtikova AN, Fito M, Schroder H. Can metabolically healthy obesity be explained by diet, genetics, and inflammation? Molecular nutrition & food research. 2015; 59(1):75–93. [PubMed: 25418549]
14. Phillips CM, Dillon C, Harrington JM, McCarthy VJ, Kearney PM, Fitzgerald AP, et al. Defining metabolically healthy obesity: role of dietary and lifestyle factors. PloS one. 2013; 8(10):e76188. [PubMed: 24146838]
15. Camhi SM, Crouter SE, Hayman LL, Must A, Lichtenstein AH. Lifestyle Behaviors in Metabolically Healthy and Unhealthy Overweight and Obese Women: A Preliminary Study. PloS one. 2015; 10(9):e0138548. [PubMed: 26383251]
16. Bell LK, Edwards S, Grieger JA. The Relationship between Dietary Patterns and Metabolic Health in a Representative Sample of Adult Australians. Nutrients. 2015; 7(8):6491–505. [PubMed: 26251918]
17. Camhi SM, Whitney Evans E, Hayman LL, Lichtenstein AH, Must A. Healthy eating index and metabolically healthy obesity in U.S. adolescents and adults. Preventive medicine. 2015; 77:23–7. [PubMed: 25937589]
18. Park YM, Steck SE, Fung TT, Zhang J, Hazlett LJ, Han K, et al. Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) style diet, and metabolic health in U.S. adults. Clinical nutrition (Edinburgh, Scotland). 2016
19. Hankinson AL, Daviglus ML, Van Horn L, Chan Q, Brown I, Holmes E, et al. Diet composition and activity level of at risk and metabolically healthy obese American adults. Obesity (Silver Spring). 2013; 21(3):637–43. [PubMed: 23592673]
20. Kimokoti RW, Judd SE, Shikany JM, Newby PK. Food intake does not differ between obese women who are metabolically healthy or abnormal. The Journal of nutrition. 2014; 144(12):2018–26. [PubMed: 25411036]
21. Park YM, Steck SE, Fung TT, Zhang J, Hazlett LJ, Han K, et al. Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes. International journal of obesity. 2016; 40(10):1541–9. [PubMed: 27339604]
22. Janiszewski PM, Ross R. Effects of weight loss among metabolically healthy obese men and women. Diabetes care. 2010; 33(9):1957–9. [PubMed: 20573755]
23. Kantartzis K, Machann J, Schick F, Rittig K, Machicao F, Fritsche A, et al. Effects of a lifestyle intervention in metabolically benign and malign obesity. Diabetologia. 2011; 54(4):864–8. [PubMed: 21174075]
24. Ruiz JR, Ortega FB, Labayen I. A weight loss diet intervention has a similar beneficial effect on both metabolically abnormal obese and metabolically healthy but obese premenopausal women. Annals of nutrition & metabolism. 2013; 62(3):223–30. [PubMed: 23571719]
25. Shin MJ, Hyun YJ, Kim OY, Kim JY, Jang Y, Lee JH. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. International journal of obesity. 2006; 30(10):1529–34. [PubMed: 16552406]

26. Liu RH, Wharton S, Sharma AM, Ardern CI, Kuk JL. Influence of a clinical lifestyle-based weight loss program on the metabolic risk profile of metabolically normal and abnormal obese adults. Obesity (Silver Spring). 2013; 21(8):1533–9. [PubMed: 23696195]
27. United States. National Center for Health Statistics. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; Hyattsville, MD, Washington, DC: 1994.
28. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public health nutrition. 2014; 17(8):1825–33. [PubMed: 24107546]
29. Wirth MD, Shivappa N, Davis L, et al. Construct validation of the Dietary Inflammatory Index among African Americans. J Nutr Health Aging. 2016:1–5.
30. Centers for Disease Control and Prevention. Loboratory procedures used for the third national health and nutrition examination survery (nhanes iii), 1988–1994 1996. Available from: https://wwwn.cdc.gov/nchs/nhanes/nhanes3/manualsandreports.aspx
31. Centers for Disease Control and Prevention. NCHS Surverys Linked to NDI Mortality Data. 2017. Available from: https://www.cdc.gov/nchs/data-linkage/mortality.htm
32. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007; 116(9):1081–93. [PubMed: 17671237]
33. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120(16):1640–5. [PubMed: 19805654]
34. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation. 2003; 107(3):391–7. [PubMed: 12551861]
35. Graffouillere L, Deschasaux M, Mariotti F, Neufcourt L, Shivappa N, Hebert JR, et al. Prospective association between the Dietary Inflammatory Index and mortality: modulation by antioxidant supplementation in the SU.VI.MAX randomized controlled trial. Am J Clin Nutr. 2016; 103(3): 878–85. [PubMed: 26864363]
36. Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nat Rev Immunol. 2008; 8(12):923–34. [PubMed: 19029988]
37. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature. 2006; 440(7086):944–8. [PubMed: 16612386]
38. Deng FE, Shivappa N, Tang Y, Mann JR, Hebert JR. Association between diet-related inflammation, all-cause, all-cancer, and cardiovascular disease mortality, with special focus on prediabetics: findings from NHANES III. Eur J Nutr. 2017; 56(3):1085–93. [PubMed: 26825592]
39. Dalzill C, Nigam A, Juneau M, Guilbeault V, Latour E, Mauriege P, et al. Intensive lifestyle intervention improves cardiometabolic and exercise parameters in metabolically healthy obese and metabolically unhealthy obese individuals. The Canadian journal of cardiology. 2014; 30(4):434–40. [PubMed: 24561010]
40. Park YM, Fung TT, Steck SE, Zhang J, Hazlett LJ, Han K, et al. Diet Quality and Mortality Risk in Metabolically Obese Normal-Weight Adults. Mayo Clinic proceedings. 2016; 91(10):1372–83. [PubMed: 27712636]
41. Stelmach-Mardas M, Walkowiak J. Dietary Interventions and Changes in Cardio-Metabolic Parameters in Metabolically Healthy Obese Subjects: A Systematic Review with Meta-Analysis. Nutrients. 2016; 8(8)
42. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. The British journal of nutrition. 2015; 113(4):665–71. [PubMed: 25639781]

43. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. The New England journal of medicine. 2004; 350(14):1387–97. [PubMed: 15070788]

44. Veeranna V, Zalawadiya SK, Niraj A, Pradhan J, Ference B, Burack RC, et al. Homocysteine and reclassification of cardiovascular disease risk. Journal of the American College of Cardiology. 2011; 58(10):1025–33. [PubMed: 21867837]

45. Boden S, Wennberg M, Van Guelpen B, Johansson I, Lindahl B, Andersson J, et al. Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study. Nutrition journal. 2017; 16(1):21. [PubMed: 28376792]

Table 1

Comparison of general characteristics with increasing tertiles for Dietary Inflammatory Index (DII) in Metabolically Healthy Overweight/Obese (MHO) and Metabolically Unhealthy Overweight/Obese (MUO) phenotypes in NHANES III follow up study at baseline, 1988–1994.

	Metabolically Healthy Overweight/Obese (MHO) phenotype					**Metabolically Unhealthy Overweight/Obese (MUO) phenotype**					**P**
Characteristics	**Overall (n=1815)**	**Tertile 1 (n=570)**	**Tertile 2 (n=611)**	**Tertile 3 (n=634)**	**P**	**Overall (n=1918)**	**Tertile 1 (n=674)**	**Tertile 2 (n=634)**	**Tertile 3 (n=610)**	**P**	**(MHO vs. MUO)**
DII	**0.57**	**(−5.08 to −0.24)**	**(−0.24 to 1.97)**	**(1.97 to 4.55)**	**<.001**	**0.38**	**(−5.19 to−0.24)**	**(−0.24 to 1.97)**	**(1.97 to 4.84)**	**<.001**	**<.001**
Proportion (%)											
Men	51	71.8	50.8	27.7	<.001	65.4	78.1	65.4	46.9	<.001	<.001
Non-Hispanic white	71.5	77.9	70.9	64.8	<.001	77.8	80.4	78.4	73.3	0.02	0.001
Educational attainment (>12 yrs)	80.6	84.2	81	76	0.03	71.9	77.8	71.7	63.5	<.001	<.001
Income (PIR>1.3)	83.2	88.2	86.6	73.1	<.001	83.1	90.3	80	75.9	<.001	0.95
Non-smoker	54.3	53.7	55.8	53.1	0.85	38.6	38.5	37.7	39.7	0.91	<.001
Moderate drinker	58.4	63.8	56	55.2	0.07	52.5	59.1	53.8	41.3	0.001	0.009
Recommended physical activity	30.5	36.2	30.8	23.6	0.04	31.6	33.2	29.9	31.3	0.7	0.53
Diabetes mellitus	2.7	2.2	2.6	3.6	0.51	16.1	16	12.4	20.6	0.02	<.001
Hypertension	14.5	14	15.6	13.6	0.81	45.8	48	43.9	44.7	0.59	<.001
Mean											
Age, yrs	41	40.6	41.1	41.3	0.48	48.7	48.9	47.5	49.8	0.38	<.001
BMI, kg/m^2	28.6	28.2	28.5	29.3	<.001	30.4	29.9	30.9	30.6	0.007	<.001
Waist circumference, cm	95.4	95.8	94.9	95.5	0.64	103.4	103.2	104.4	102.4	0.39	<.001
Fasting glucose, mg/dl	91	92	91	91	0.17	105	105	104	105	0.92	<.001
HOMA-IR	2.01	1.92	2.01	2.11	0.003	3.89	3.8	4	3.88	0.12	<.001
SBP, mmHg	119	119	119	118	0.69	131	131	131	131	0.43	<.001
DBP, mmHg	74	74	74	73	0.11	80	82	79	78	<.001	<.001
hs-CRP, mg/dl	0.29	0.26	0.28	0.34	<.001	0.34	0.32	0.34	0.38	<.001	<.001
Triglycerides, mg/dl	102	105	104	96	0.01	203	204	211	193	0.44	<.001
HDL-C, mg/dl	52	51	52	54	0.001	41	41	40	42	0.19	<.001

Data are presented as meansor proportion. P values for continuous variables represent P for trend. Variables with skewed distribution such as HOMA-IR, hs-CRP, and triglycerides were compared after log-transformation.

Abbreviations: DII, dietary inflammatory index; PIR, poverty income ratio; BMI, waist circumference; HOMA-IR, homoeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol.

Table 2

Multivariable adjusted hazard ratio (HR) and 95% CI of all-cause, cardiovascular, and cancer mortality according to the DII tertile categories in the Overweight and Obese participants in NHANES III follow up study, 1988–1994, followed up for death until December 31, 2011.

	DII Tertile 1	DII Tertile 2	DII Tertile 3	P trend	HR for a 1 SD increase in DII
No. of participants	1244	1245	1244		
No. of person years	21805	21401	21210		
Deaths from all causes, n	261	293	314		
	1.00 (ref.)	1.18(0.98–1.43)	1.18(0.90–1.55)	0.22	1.03(0.94–1.13)
CVD Deaths, n	73	81	98		
	1.00 (ref.)	2.02(1.50–2.71)	2.50(1.60–3.91)	<0.001	1.32(1.10–1.58)
*Cancer Deaths, n	67	73	69		
	1.00 (ref.)	1.09(0.71–1.67)	0.94(0.57–1.53)	0.79	0.94(0.77–1.16)

Data are presented as hazard ratio (95% confidence interval).

Abbreviations: DII, dietary inflammatory index; CVD, cardiovascular disease.

Multivariable adjusted hazard ratio is adjusted for age, sex, race/ethnicity(non-Hispanic white, non-Hispanic black, or others), educational attainment(<12 years, 12 years, or >12 years of education), income[low (poverty income ratio (PIR) ≤ 1.3), middle (1.3<PIR ≤ 3.5), and high (PIR>3.5)], smoking status(never, former, and current), level of physical activity(inactive, insufficient activity, recommended activity), and body mass index.

*Those who had a history of skin cancer were additionally excluded.

Table 3

Multivariable adjusted hazard ratio (HR) and 95% CI of all-cause, cardiovascular, and cancer mortality according to the DII tertile categories in Metabolically Healthy Overweight/Obese (MHO) and Metabolically Unhealthy Overweight/Obese (MUO) phenotypes in NHANES III follow up study, 1988–1994, followed up for death until December 31, 2011.

	Metabolically Healthy Overweight/Obese (MHO) phenotype					**Metabolically Unhealthy Overweight/Obese (MUO) phenotype**				
	DII tertile 1	**DII tertile 2**	**DII tertile 3**	**P trend**	**HR for a 1 SD increase in DII**	**DII tertile 1**	**DII tertile 2**	**DII tertile 3**	**P trend**	**HR for a 1 SD increase in DII**
No. of participants	570	611	634			674	634	610		
No. of person years	10398	11086	11478			11407	10315	9732		
Deaths from all causes, n	73	80	93			188	213	221		
	1.00 (ref.)	0.78 (0.56–1.11)	0.77 (0.50–1.20)	0.27	0.93 (0.76–1.13)	1.00 (ref.)	1.41 (1.15–1.73)	1.44 (1.11–1.86)	0.008	1.08 (0.99–1.18)
CVD Deaths, n	18	20	29			55	61	69		
	1.00 (ref.)	0.84 (0.32–2.18)	1.05 (0.56–1.98)	0.75	1.11 (0.79–1.55)	1.00 (ref.)	2.48 (1.79–3.44)	3.29 (2.01–5.37)	<0.001	1.40 (1.18–1.66)
*Cancer Deaths, n	21	20	14			46	53	55		
	1.00 (ref.)	0.86 (0.43–1.70)	0.42 (0.13–1.34)	0.12	0.75 (0.50–1.13)	1.00 (ref.)	1.20 (0.80–1.78)	1.26 (0.76–2.08)	0.35	1.05 (0.85–1.30)

Data are presented as hazard ratio (95% confidence interval).

Abbreviations: DII, dietary inflammatory index; CVD, cardiovascular disease.

Multivariable adjusted hazard ratio is adjusted for age, sex, race/ethnicity(non-Hispanic white, non-Hispanic black, or others), educational attainment(<12 years, 12 years, or >12 years of education), income[low (poverty income ratio (PIR) ≤ 1.3), middle (1.3<PIR ≤ 3.5), and high (PIR>3.5)], smoking status(never, former, and current), level of physical activity(inactive, insufficient activity, recommended activity), and body mass index.

*Those who had a history of skin cancer were additionally excluded.

Table 4

Subgroup analyses of the association between a 1 SD increment in the DII and the risk of all-cause and CVD mortality in Metabolically Unhealthy Overweight/Obese (MUO) phenotypes in NHANES III follow up study, 1988–1994, followed up for death until December 31, 2011.

		All-cause mortality			CVD mortality		
	No. of participants	**No. of deaths**	**Multivariable-adjusted HR (95% CI)for a 1 SD increase in DII**	**P interaction**	**No. of deaths**	**Multivariable-adjusted HR (95% CI)for a 1 SD increase in DII**	**P interaction**
Age, y				0.64			0.04
< 65	1393	232	0.99 (0.82–1.19)		53	1.72 (1.15–2.58)	
≥ 65	525	390	1.14 (1.00–1.31)		132	1.31 (1.17–1.49)	
Sex				0.34			0.33
Men	1100	360	1.04 (0.94–1.16)		105	1.31 (0.95–1.82)	
Women	818	262	1.16 (0.99–1.36)		80	1.59 (1.32–1.92)	
Race/ ethnicity				0.54			0.47
Non-Hispanic white	825	353	1.08 (0.96–1.21)		112	1.47 (1.18–1.84)	
Others	1093	269	1.17 (0.98–1.39)		73	1.34 (0.98–1.83)	
Body mass index, kg/m^2				0.23			0.03
< 30	1034	389	1.11 (0.99–1.24)		119	1.18 (1.03–1.35)	
≥ 30	884	233	1.04 (0.87–1.24)		66	1.74 (1.21–2.50)	
Smoking status				0.64			0.87
Never-smoker	901	252	1.16 (0.99–1.34)		76	1.54 (1.24–1.90)	
Ever-smoker	1017	370	1.08 (0.96–1.23)		109	1.42 (1.10–1.82)	
Recommended physical activity				0.54			0.53
Yes	564	213	1.16 (0.98–1.37)		67	1.58 (1.10–2.26)	
No	1354	409	1.02 (0.92–1.14)		118	1.20 (1.05–1.37)	

Abbreviations: DII, dietary inflammatory index; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

Multivariable models adjusted for age, sex, race/ethnicity(non-Hispanic white, non-Hispanic black, or others), educational attainment(<12 years, 12 years, or >12 years of education), income[low (poverty income ratio (PIR) ≤ 1.3), middle (1.3<PIR ≤ 3.5), and high (PIR>3.5)], smoking status(never, former, and current), level of physical activity(inactive, insufficient activity, recommended activity), and body mass index.