



Original article

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



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ARTICLE INFO

Article history:

Received 23 August 2017

Accepted 2 April 2018

Keywords:

National Health and Nutrition Examination

Survey III

Dietary inflammatory index

Overweight

Obesity

Metabolic health

Mortality

SUMMARY

Background & 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 \geq 25 kg/m²) 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-h dietary recalls. Metabolically unhealthy status was 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 \geq 30 kg/m²), 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.

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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.

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1. 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 TNF α , 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.

2. Materials and methods

2.1. Study population

Data from individuals participating in the National Health and Nutrition Examination Survey (NHANES) III from 1988 to 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 ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$) or obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) adults aged 20–90 years at baseline based on measured height and weight, who had complete data on mortality follow-up, a single 24-h 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 $>5000 \text{ kcal/d}$) ($n = 89$), $\text{BMI} > 50 \text{ kg/m}^2$ ($n = 17$) or were pregnant or lactating ($n = 25$) also were excluded. Finally, we analyzed data from a total of 3733 individuals.

2.2. 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-1 β , 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].

2.3. 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 0.01 kg and 0.1 cm; 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 radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). Triglycerides and HDL-C levels were measured using a Hitachi 704 analyzer (Boehringer-Mannheim Diagnostics, Germany). Latex-enhanced nephelometry (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 6 h 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) \times fasting insulin (IU/mL)/405] greater than the 90th percentile, systolic/diastolic BP $\geq 130/85$ 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 90th percentile) [9].

2.4. 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].

2.5. Statistical analysis

All statistical analyses were conducted using SAS[®] software, version 9.4 (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 \pm 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 than 0.05 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 [$1.3 < \text{PIR} \leq 3.5$], and high [$\text{PIR} > 3.5$]), 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 ($3 \leq$ 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 $\geq 130/85$ 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.

3. 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 Supplementary 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 Supplementary 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) ($P_{\text{trend}} < 0.001$) 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 Supplementary 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) ($P_{\text{trend}} = 0.008$) for all-cause mortality, and 2.48 (95% CI 1.79–3.44) and 3.29 (95% CI 2.01–5.37) ($P_{\text{trend}} \leq 0.001$) 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

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.

Characteristics	Metabolically Healthy Overweight/Obese (MHO) phenotype					Metabolically Unhealthy Overweight/Obese (MUO) phenotype					P (MHO vs. MUO)
	Overall	Tertile 1	Tertile 2	Tertile 3	P	Overall	Tertile 1	Tertile 2	Tertile 3	P	
	(n = 1815)	(n = 570)	(n = 611)	(n = 634)		(n = 1918)	(n = 674)	(n = 634)	(n = 610)		
DII	0.57	(−5.08 to −0.24)	(−0.24 to 1.97)	(1.97–4.55)	<0.001	0.38	(−5.19 to −0.24)	(−0.24 to 1.97)	(1.97–4.84)	<0.001	<0.001
Proportion (%)											
Men	51	71.8	50.8	27.7	<0.001	65.4	78.1	65.4	46.9	<0.001	<0.001
Non-Hispanic White	71.5	77.9	70.9	64.8	<0.001	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	<0.001	<0.001
Income (PIR > 1.3)	83.2	88.2	86.6	73.1	<0.001	83.1	90.3	80	75.9	<0.001	0.95
Non-smoker	54.3	53.7	55.8	53.1	0.85	38.6	38.5	37.7	39.7	0.91	<0.001
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	<0.001
Hypertension	14.5	14	15.6	13.6	0.81	45.8	48	43.9	44.7	0.59	<0.001
Mean											
Age, yrs	41	40.6	41.1	41.3	0.48	48.7	48.9	47.5	49.8	0.38	<0.001
BMI, kg/m ²	28.6	28.2	28.5	29.3	<0.001	30.4	29.9	30.9	30.6	0.007	<0.001
Waist circumference, cm	95.4	95.8	94.9	95.5	0.64	103.4	103.2	104.4	102.4	0.39	<0.001
Fasting glucose, mg/dl	91	92	91	91	0.17	105	105	104	105	0.92	<0.001
HOMA-IR	2.01	1.92	2.01	2.11	0.003	3.89	3.8	4	3.88	0.12	<0.001
SBP, mmHg	119	119	119	118	0.69	131	131	131	131	0.43	<0.001
DBP, mmHg	74	74	74	73	0.11	80	82	79	78	<0.001	<0.001
hs-CRP, mg/dl	0.29	0.26	0.28	0.34	<0.001	0.34	0.32	0.34	0.38	<0.001	<0.001
Triglycerides, mg/dl	102	105	104	96	0.01	203	204	211	193	0.44	<0.001
HDL-C, mg/dl	52	51	52	54	0.001	41	41	40	42	0.19	<0.001

Data are presented as means or 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, body mass index; HOMA-IR, homeostasis 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	21 805	21 401	21 210		
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)
^a 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.

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

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).

4. Discussion

In this nationally representative study of US adults, higher DII score was associated with an increased risk of all-cause mortality

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	10 398	11 086	11 478			11 407	10 315	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)
^a 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.

^a 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.

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

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 \geq 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.

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 and funding sources

This research was supported in part by the Intramural Program in the NIH, National Institute of Environmental Health Sciences. Drs. Shivappa and Hébert were supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases.

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)TM from the University of South Carolina in order to develop computer and smart phone applications for patient counseling 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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnu.2018.04.002>.

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