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Diet quality is associated with circulating C-reactive protein but not irisin levels in humans

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Abstract

Objective—Adherence to a healthy diet has been shown to decrease the incidence of obesity and associated comorbidities. C-reactive protein (CRP) is an established inflammatory marker and irisin was recently identified as a molecule which may play a role in energy regulation and obesity but whether diet alters irisin levels remains unknown. We aimed to investigate the association between circulating irisin, leptin, and CRP levels and dietary quantity and quality using the Alternate Healthy Eating Index (AHEI) and the Alternate Mediterranean Diet Score (aMED).

Materials/Methods—The study evaluated dietary data and biomarker levels of 151 participants between 2009 and 2011 (71 male vs. 80 female, over 35 years old, obese 43.7%). AHEI and

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Conflict of Interest

None of the authors reported a conflict of interest.

Author contributions

KHP and CSM performed study design and statistical evaluations; LZ, CRD, JAC collected data; KHP, LZ, PP, and CSM wrote manuscript. All authors contributed to the data interpretation and editing and reviewing manuscript.

aMED scores were calculated based on data derived from self-administered 110-item food-frequency questionnaires estimating usual nutrient intake over the past year. Cross-sectional associations between dietary quantity, quality, body composition by bioelectric impedance, and biomarker levels including irisin, leptin, and CRP after fasting were assessed.

Results—CRP, but not irisin, was negatively correlated with AHEI ($r = -0.34$) and aMED ($r = -0.31$). Irisin was positively correlated with BMI ($r = 0.22$), fat mass ($r = 0.21$), waist circumference ($r = 0.24$), waist-hip ratio ($r = 0.20$), leptin ($r = 0.32$), and CRP ($r = 0.25$). Participants with the highest AHEI scores tended to have 11.6% lower concentrations of irisin (P for trend = 0.09), but they were not significant after adjustment for potential confounders. Better diet quality was associated with lower CRP concentrations (P for trend = 0.02) in multivariate model. Percentage of energy from carbohydrate was inversely associated with CRP.

Conclusions—Unlike CRP, irisin is not associated with dietary quality or quantity.

Keywords

irisin; dietary pattern; Alternate Healthy Eating Index; Mediterranean Diet; C-reactive protein

Introduction

The growing prevalence of obesity has been associated with the increasing incidence of cardiovascular diseases, cancer, and all-cause mortality [1–3]. Mechanistically, weight gain and obesity result from an imbalance between energy intake and expenditure with the nutritional composition of energy intake likely playing an important role in determining outcomes. The Alternate Healthy Eating Index (AHEI) [4] and Mediterranean Diet Score (MDS) [5] are well-validated and widely used dietary quality assessment tools that have proven useful in quantifying nutritional intake. Adherence to a healthy diet as indicated by higher AHEI and MDS scores has previously been associated with reduction of risk for cardiovascular disease and mortality [5–9]. The alternate Mediterranean Diet Score (aMED), which is based on the original MDS by Trichopoulou *et al.* [5], was designed to be used with a food frequency questionnaire developed in the United States [6,10,11].

Leptin, a well-known adipose tissue secreted hormone, has been found to play a major role in energy metabolism, inflammation, and atherosclerosis [12,13]. Previous studies suggest that leptin concentrations are positively correlated and/or associated with fat intake [14] or a western-pattern diet [15]. In addition, it has been shown that C-reactive protein (CRP) is negatively associated with adherence to Mediterranean or AHEI dietary patterns [6,16–18], and a dietary intervention-based Mediterranean dietary pattern resulted in reductions in plasma CRP and/or leptin. [16,18,19].

Irisin, a recently identified myokine, is thought to play an important role in energy regulation and the development of obesity. Although previous human studies [20–25] have suggested a correlation between irisin and metabolic parameters associated with obesity, the results are inconsistent. To date, no human studies have examined the relationship between irisin and dietary quality, and/or energy and macronutrient intake. Considering the possible role of irisin in glucose metabolism and obesity, it is important to explore the association

between irisin and dietary pattern, which is one of the modifiable factors predisposing to obesity or cardiometabolic diseases.

This study investigates the relationship between irisin and dietary quantity and quality as measured by the AHEI and aMED, and compares this to similar data on adipokine levels (i.e. leptin) and the inflammatory marker CRP.

Materials and Methods

Study design and population

A cross-sectional study was conducted in 151 Caucasian and African American individuals (71 male vs. 80 female, over 35 years old, 43.7% with BMI ≥ 30) who were part of the study examining any predictors of health disparities. They were recruited through advertising (radio, newspapers, and fliers) in the Boston area over 18 months between 2009 and 2011. Subjects with a history of myocardial infarction, stroke, those who carried a diagnosis of diabetes mellitus, active IV drug use, hepatitis or cirrhosis, those on dialysis or long-term steroid use, and those undergoing current treatment for cancer or active infection (other than brief antibiotic therapies) were excluded from enrollment. Adequate plasma samples were not available for all subjects, so 148 samples were analyzed for irisin, 149 for CRP, and 149 for leptin.

This study was approved by the Beth Israel Deaconess Medical Center (BIDMC) Committee on Clinical Investigations and Institutional Review Board, in accordance with the Helsinki Declaration of 1975 as revised in 1983. All participants gave written informed consent prior to participation in the study. As part of the informed consent process, participants' rights as research subjects, exceptions to confidentiality, and possible risks involved were clearly explained.

Assessment of biomarkers

Participants fasted overnight before arriving to the Clinical Research Center of BIDMC for their visit. Blood samples were collected from participants and the serum and plasma were stored at -80°C until they were used to analyze irisin, leptin, and CRP levels. Leptin was measured by radioimmunoassay (RIA) (Millipore, Billerica, MA, USA). Irisin (EK-067-52, Phoenix Pharmaceuticals, CA, USA) was measured by ELISA. CRP was measured with the Roche Cobas c311 clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA). In this study, inter-assay CVs were, 3.6–6.2% for leptin, $<15\%$ for irisin, and 1.7–11.5% for CRP.

Dietary assessment

Dietary intake of participants was assessed by using 110-item self-administered Block Food Frequency Questionnaire (FFQ) (NutritionQuest, Berkeley, CA), which have been validated in previous studies [26,27], following instructions from study staff. For each food item in FFQ, study participants answered two groups of questions, first on the average frequency each food item had been consumed during the past a year and second on the amount of the food item consumed per each intake. For the frequency question, the participants chose an

answer from among 9 responses ranging from “never” to “every day”. For the question on the amount of food consumption, the participants had to choose the portion size from among standardized pictures included in the FFQ.

Usual intake of nutrient was calculated by multiplication of the average consumption frequency of each food item during the prior year by its pre-specified common serving size, and then summed according to the food groups of AHEI [4] and aMED [6], as calculated in previous studies [5,7]. The AHEI score was calculated from the FFQ on the basis of each of the following nine components: vegetables except potatoes, fruit, cereal fiber, nuts and soy, ratio of white to red meat, trans fat, ratio of polyunsaturated to saturated fatty acids, multivitamin use, and alcohol consumption. The aMED score was calculated from the FFQ on the basis of following nine groups: Vegetables except potatoes, legumes, fruits, nuts, whole-grain products, fish, red and processed meats, ratio of monounsaturated to saturated fat, and alcohol. The aMED score is different from the original MDS in that it was modified to exclude potato products from the vegetable group, separate fruits and nuts into two groups, eliminate the dairy group, include whole-grain products only, and include only red and processed meats in the meat group. Participants with intake above the median intake received 1 point for these categories; otherwise, they received 0 points. Red and processed meat consumption below the median received 1 point. We assigned 1 point for alcohol intake between 1.5–2.5 drinks/day for men and 0.5–1.5 drinks/day for women.

Assessment of other variables

Anthropometry and body composition was measured by a well-trained dietician. Height was measured by a wall-mounted stadiometer to the nearest 0.1cm. Weight was measured without shoes using a calibrated digital electric scale to the nearest 0.1kg. Bioelectrical impedance analysis (BIA) was performed with subjects lying in a supine position as previously described [28] using a Quantum II bioelectrical impedance analyzer (RJL Systems, Clinton Township, MI, USA). Measurements were performed during the fasting state prior to blood sampling, with subjects wearing a standard hospital gown and pajama bottoms. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and waist-hip ratio (WHR) was determined by proportion of waist to hip circumference. Waist circumference was measured along the superior border of the iliac crest.

Statistical analysis

Comparisons between genders and races were made using the student's t-test for continuous variables. AHEI and aMED were categorized into tertiles. Spearman's correlation coefficients were checked to evaluate the relationship between irisin and dietary indices, as well as anthropometric measurements and other biomarkers, such as leptin and CRP. Mean values of variables across tertile groups were compared by one-way analysis of variance and trends of mean across the tertile groups were estimated via a linear regression model. Biomarker concentrations were logarithmically transformed to improve normality.

Simple and multivariate adjusted linear regression models were used to examine the associations of irisin, leptin, and CRP concentrations across tertiles of dietary pattern indices. In multivariate analysis, potential confounders such as gender, BMI, WHR, and

percent body fat were adjusted for. Significantly associated biomarkers were also included in the final models.

All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Descriptive statistics of the study variables for males and females are presented in Table 1. The means of AHEI and aMED scores were similar across genders. Compared to males, females had higher leptin concentrations (23.05 ± 2.23 ng/ml for females vs. 9.49 ± 3.81 ng/ml for males, $P < 0.001$). There was no difference in irisin concentration between the two groups. Compared to Caucasians, African-Americans had higher irisin (166.0 ± 1.4 ng/ml vs. 196.5 ± 1.4 ng/ml, $P = 0.005$), leptin (11.7 ± 3.3 ng/ml vs. 18.9 ± 3.1 ng/ml, $P = 0.01$), and CRP (1.09 ± 3.2 mg/L vs. 1.67 ± 3.3 mg/L, $P = 0.03$) levels. Irisin levels in African-Americans were higher than in Caucasians after adjusting for BMI ($P = 0.02$). This significance of difference remained unchanged after adjustment for fat free mass, age, and gender ($P = 0.005$, data not shown) as well as BMI, age, and gender ($P = 0.01$, data not shown).

Correlations between dietary quality scores and biomarkers

Spearman correlation coefficients for the association between AHEI and aMED score, anthropometric measurements, and biomarkers are presented in Table 2. Both dietary quality scores were positively correlated with total energy intake ($r = 0.25$ with AHEI, $r = 0.31$ with aMED) and negatively correlated with BMI ($r = -0.30$ with AHEI, $r = -0.32$ with aMED), waist circumference ($r = -0.33$ with AHEI, $r = -0.32$ with aMED), WHR ($r = -0.29$ with AHEI, $r = -0.20$ with aMED), fat mass ($r = -0.23$ with AHEI, $r = -0.25$ with aMED), and fat-free mass ($r = -0.22$ with AHEI, $r = -0.17$ with aMED). Among the biomarkers, CRP was negatively correlated with AHEI ($r = -0.34$) and aMED ($r = -0.31$), while irisin and leptin showed no significant correlation with either score. Like leptin, irisin was positively correlated with anthropometric measurements; BMI ($r = 0.22$, $P = 0.008$), body fat mass ($r = 0.21$, $P = 0.01$), waist circumference ($r = 0.24$, $P = 0.003$), and WHR ($r = 0.20$, $P = 0.02$). Amongst the three biomarkers, irisin was found to be positively correlated with leptin ($r = 0.32$) and CRP ($r = 0.25$).

Associations between dietary quality scores and biomarkers

Mean anthropometric measurements, biomarker concentrations and nutritional intake across tertiles of AHEI and aMED scores are presented in Table 3 with the highest tertile representing the best diet scores. We found that waist circumference, WHR, fat mass CRP, and BMI were lower in the higher tertile groups of AHEI and aMED. Percentage of body fat was lower in the higher tertile group of aMED. By contrast, percentage of fat-free mass and total calorie intake increased with higher scores of AHEI and aMED. Percentage of energy intake from the three main groups of macronutrients was not different across the tertiles of AHEI and aMED scores.

Subjects with the highest AHEI and aMED scores did not have lower concentrations of irisin (3rd vs. 1st tertile = 171.3 ± 1.4 ng/ml vs. 193.8 ± 1.5 ng/ml, P for trend = 0.096 for AHEI,

178.2±1.46ng/ml vs. 187.2±1.36ng/ml, P for trend = 0.49 for aMED) and leptin (3rd vs. 1st tertile = 13.5±3.3ng/ml vs. 16.9±2.95ng/ml, P for trend = 0.34 for AHEI, 12.9±3.35ng/ml vs. 18.4±2.87ng/ml, P for trend = 0.14 for aMED) but had significantly higher concentrations of CRP (3rd vs. 1st tertile = 0.92±3.02mg/L vs. 2.19±3.03mg/L, P for trend = <0.001 for AHEI, 0.83±2.73mg/L vs. 2.09±3.37mg/L, P for trend = <0.001 for aMED)..

Multivariate models were employed to better examine the pattern of biomarker concentrations across the tertiles of AHEI and aMED scores (Table 4). Mean irisin concentrations did not show a statistically significant difference in any of the adjusted models, while mean CRP concentrations showed statistically significant differences in all models. In the gender-adjusted model, higher scores of AHEI and aMED were associated with lower leptin concentrations with marginal significance (P for trend = 0.08 for AHEI and 0.06 for aMED), but this association did not hold after adjustment for anthropometric measurements such as BMI, WHR, fat free mass, or percentage of body fat.

Beta (β) coefficients quantifying the relationship between dietary index scores and log-transformed biomarkers are shown in Table 5. AHEI and aMED scores showed a negative relationship with leptin in the age and gender-adjusted model (β = -0.02, P = 0.02 for AHEI, β = -0.08, P = 0.07 for aMED), but this relationship did not persist after adjusting for gender and anthropometric measurements. Irisin concentrations were not associated with dietary index scores in this analysis. CRP concentrations showed a negative association with AHEI and aMED, independent of gender, age, race, BMI or other biomarkers.

Association between dietary quantity and biomarkers

To better evaluate the association between irisin and intake of total energy and macronutrients, further analyses were performed using multiple linear regressions with AHEI and aMED scores as continuous variables, and using the energy partition and density models [29,30]. Finally, in the energy partition and density model, the percentage of daily calories provided by carbohydrates was negatively associated with log CRP level adjusted for body fat mass and total calorie intake (standardized beta = -0.15, P = 0.03, data not shown). Total energy intake and macronutrient composition of the diet were not associated with irisin or leptin concentrations (data not shown).

Discussion

In this study, we found an inverse association between CRP and diet quantity as well as diet quality, i.e. dietary patterns, using the AHEI and aMED scores, whereas irisin was not associated with these dietary indices. We also found that neither energy intake from specific macronutrients nor total energy intake was associated with irisin concentrations.

Previous studies have examined the association between dietary quality and adipokines [16,31,32], markers of inflammation [6,33], and mortality from cardiovascular diseases [8], finding that higher AHEI or aMED scores were associated with higher adiponectin concentrations, with lower concentrations of biomarkers of inflammation and endothelial dysfunction, and decreased mortality risk from cardiovascular diseases, respectively. Our study confirmed a significant inverse association between CRP levels and healthy eating

patterns. In contrast to this association, irisin was not found to have any associations with these dietary indices suggesting that its effects are likely exerted in a nutrition-independent fashion. Indeed, irisin has been linked to acute exercise [20] and energy expenditure in humans[34], and has been shown to directly influence glucose metabolism in mice [35].

Our study showed no association between leptin concentration and dietary variables after adjustment for anthropometric indices such as BMI, WHR, or percentage of body fat, while it showed an inverse association between leptin and aMED score in a gender-adjusted model with marginal significance. A previous study analyzing data from the third National Health and Nutrition Examination Survey also reported no association between leptin and dietary patterns in a US cohort [36]. Recently published study also reported the little effect of the Mediterranean dietary intervention on the concentration of adipokines without weight loss[37]. This indicates that the association between leptin concentration and dietary pattern may be mediated by BMI or body fat mass rather than dietary quality per se.

Although the association between dietary patterns or lifestyle modification and CRP has been investigated in epidemiological studies [6,16,17,38–42], studies on the association between specific macronutrient and CRP are limited. In previous studies, glycemic load [43–45], dietary fiber [46], and saturated fat intake [43,47] were shown to be associated with CRP. In our study, percentage of daily calories provided by carbohydrates was negatively associated with log CRP level after adjustment for body fat mass and total calorie intake (standardized beta regression coefficient = -0.15 , $P = 0.03$, data not shown).

Irisin was positively correlated with CRP and leptin, as well as anthropometric measurements such as BMI, body fat mass, waist circumference, and WHR, suggesting that this hormone could play an important role in the delicate balance of energy metabolism. Though several studies on irisin have been performed [20–24,34,35,48–51] and irisin is hypothesized to play an important role in human metabolism[52–54], about the physiology of this hormone has yet to be fully characterized including how it is regulated and how it might be involved in the development of obesity and its comorbidities. Although previous studies have reported inconsistent results on the associations between irisin and diabetic status, obesity status, or insulin resistance, the positive association between irisin and BMI is the most robust finding in human studies [20,22,23,49]. Our results are in agreement with these studies indicating a positive correlation between irisin and anthropometric variables including BMI, body fat mass, waist circumference, and WHR. Additionally, we found that irisin concentration is positively correlated with leptin and CRP. Other studies[20,22] have also indicated that irisin might be positively correlated with leptin and CRP, but these correlations did not reach significance in these smaller previous studies [20,22].

Importantly, the strength of present study is that this is the first study to examine the association of irisin with diet, specifically dietary quality, energy intake, and macronutrient composition. Moreover, reliable, previously validated, high quality assays to measure CRP and irisin were conducted by laboratory personnel blinded to study hypothesis and sample identity, eliminating bias from these sources. The novel finding on the race-related difference of irisin levels is an additional strength of this study. To date, no study has investigated whether racial differences of irisin levels exist. We found that Caucasians have

lower irisin levels than African-Americans, and that this association persists even after adjustment for BMI, age, gender, CRP, and leptin ($P=0.02$, data not shown) in the multivariate model. Moreover, this association also remained significant using fat free mass or fat mass as covariates instead of BMI in the multivariate model ($P=0.02$, data not shown). These data, if confirmed, suggest that race is an independent and significant predictor of irisin levels even after considering the differences in body composition between Caucasians and American-Africans. Future study should focus on race-related association in irisin level.

Though this study is somewhat limited by its relatively small sample size, the number of subjects included would provide more than 80% power to demonstrate associations at the conventional $\alpha = 0.05$ level when such associations are at least of moderate strength ($r > 0.20$). Thus, it is adequately powered to demonstrate the expected association between dietary patterns and CRP [6,16,17].

Considering the limitations of the indirect methods of measurements, we used validated questionnaires for the measurement of dietary intake[26,27] and assessment tools for body composition[55,56].

In conclusion, irisin is not associated with dietary quality, total energy intake, or macronutrient content of the diet, while CRP was inversely associated with dietary quality and quantity. Thus, the significant correlations between irisin, important anthropometric measurements, and adipokines suggest that irisin may be associated with obesity and cardiovascular disease risk independent of dietary intake, likely mediating the effect of exercise only. The race-related difference in irisin levels found in the present study should be confirmed and its etiology elucidated in future studies.

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Abbreviations

aMED	Alternate Mediterranean Diet Score
AHEI	Alternate Healthy Eating Index
BMI	Body mass index
MDS	Mediterranean Diet Score
BIDMC	Beth Israel Deaconess Medical Center
FFQ	Food Frequency Questionnaire
WHR	waist-hip ratio

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Table 1

General characteristics of the study subjects

	Gender			Race			
	Males (n=71)	Females (n=80)	<i>p^a</i>	<i>p^b</i>	Caucasians (n=72)	African- Americans (n=79)	All (n=151)
Age (y)	46.3±4.1	44.7±4.3	0.02	0.02	45.26±4.2	45.62±4.4	0.61 0.5 45.5±4.3
Gender, Female (%)	NA	NA			44.4	60.8	0.05
Race, White (%)	40.0	56.3	0.05		NA	NA	47.7
Smoking status (%)			0.87				0.004
Never	50.0	46.5			62.5	35.4	48.3
Former	20.0	19.7			13.9	25.3	19.9
Current	30.0	33.8			23.6	39.2	31.8
Irisin (ng/ml) <i>c,d</i>	182.5±1.4	180.0±1.5	0.82	0.58	166.0±1.4	196.5±1.4	0.005 0.02 181.2±1.4
Leptin (ng/ml) <i>c,d</i>	9.5±3.8	23.1±2.2	<0.001	<0.001	11.7±3.3	18.9±3.1	0.01 0.16 15.1±3.2
CRP (mg/L) <i>c,d</i>	1.11±3.3	1.64±3.2	0.11	0.16	1.09±3.2	1.67±3.3	0.03 0.34 1.36±3.3
BMI (kg/m ²)	29.2±6.2	31.1±8.2	0.11	-	28.6±6.5	31.7±7.8	0.01 - 30.2±7.4
Fat mass (%)	22.1±8.1	37.3±8.0	<0.001	<0.001	27.4±9.9	32.6±11.6	0.003 0.09 30.1±11.1
Fat mass (kg)	21.4±11.3	33.2±15.0	<0.001	<0.001	24.4±13.3	30.6±15.2	0.008 0.38 27.6±14.6
Fat-free mass (%)	78.2±8.5	62.7±8.0	<0.001	<0.001	72.9±10.3	67.4±11.6	0.003 0.07 70.0±11.3
Fat-free mass (kg)	70.1±11.6	52.0±8.6	<0.001	<0.001	61.2±13.6	59.8±13.5	0.53 0.04 60.5±13.5
Abdominal circumference (cm)	100.4±18.1	99.96±16.9	0.87	0.001	98.7±16.9	101.5±17.8	0.32 0.01 101.2±17.4
WHR	0.96±0.08	0.89±0.07	<0.001	<0.001	0.92±0.09	0.92±0.09	0.69 0.15 0.92±0.08
AHEI	43.5±12.7	46.0±11.7	0.21	0.08	46.3±11.7	43.4±12.5	0.14 0.40 44.8±12.2
aMED	4.0±2.1	4.2±2.0	0.51	0.23	4.3±2.0	4.0±2.1	0.29 0.76 4.1±2.1

Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-hip ratio; AHEI, Alternate Healthy Eating Index; aMED, alternate Mediterranean Dietary Score.

Data are shown as mean ± SD or %

^a *P* values from t-test for continuous variables and chi-square test for categorical variables.^b *P* values from by ANCOVA for continuous variables, adjusted for BMI.^c Log-transformed values were used for comparison.

The number of subjects with missing values for insulin, leptin, and CRP were 3, 2 and 2, respectively.
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Table 2

Spearman correlation coefficients (r) between studied biomarkers and dietary quality scores, dietary intake, and anthropometric measurements

	Irisin (ng/ml)		CRP (mg/L)		Leptin (ng/ml)	
	r	P	r	P	r	P
Age (years)	-0.01	0.89	0.05	0.57	-0.01	0.93
BMI (kg/m ²)	0.22	0.008	0.57	<0.001	0.54	<0.001
Waist-hip ratio	0.2	0.02	0.31	<0.001	0.17	0.04
Waist circumference (cm)	0.24	0.003	0.56	<0.001	0.51	<0.001
Fat mass (%)	0.14	0.09	0.51	<0.001	0.56	<0.001
Fat-free mass (%)	-0.14	0.09	-0.51	<0.001	-0.56	<0.001
Fat mass (kg)	0.21	0.01	0.57	<0.001	0.6	<0.001
Fat-free mass (kg)	0.12	0.16	0.07	0.38	-0.02	0.84
AHEI	-0.12	0.15	-0.34	<0.001	-0.13	0.13
aMDS	-0.05	0.54	-0.31	<0.001	-0.1	0.23
E _{tot} (kcal/d)	-0.01	0.89	-0.12	0.14	-0.1	0.21
E _{fat%}	-0.01	0.93	0.13	0.11	0.14	0.09
E _{pro%}	-0.05	0.56	0.07	0.4	0	0.96
E _{CHO%}	0.02	0.85	-0.14	0.08	-0.06	0.45
pctaleh	-0.04	0.59	-0.04	0.61	-0.12	0.15
Alcohol (drinks/day)	-0.04	0.64	-0.04	0.62	-0.11	0.19
PA (MET•hr/week)	-0.16	0.051	-0.3	<0.001	-0.21	0.01
Irisin(ng/ml)	-	-	0.25	0.002	0.32	<0.001
CRP(mg/L)	0.25	0.002	-	-	0.48	<0.001
Leptin(ng/ml)	0.32	<0.001	0.48	<0.001	-	-

Abbreviation: PA, Level of physical activity; AHEI, Alternate Healthy Eating Index; aMDS, alternate Mediterranean Dietary Score; E_{tot}, Total energy intake (kcal/d); E_{pro%}, percentage of daily calories provided by proteins; E_{CHO%}, percentage of daily calories provided by carbohydrate; and E_{fat%}, percentage of daily calories provided by dietary fat.

Table 3
General characteristics and biomarker levels of 151 subjects by tertiles (T) of average AHEI and aMED scores

	AHEI				aMED			
	T1 (n=50)	T2 (n=51)	T3 (n=50)	P for trend ^a	T1 (n=55)	T2 (n=57)	T3 (n=39)	P for trend ^a
AHEI	31.64±5.2	44.36±2.48	58.42±7.31	<0.001	33.71±7.23	46.24±6.02	58.36±9.29	<0.001
aMED	2.06±1.46	4.29±1.2	5.92±1.41	<0.001	1.89±1.07	4.49±0.5	6.72±0.83	<0.001
Age (y)	45.34±4.06	46.14±5.37	44.86±3.34	0.58	45.6±3.57	45.8±5.6	44.72±2.6	0.38
WHR	0.95±0.08	0.92±0.09	0.90±0.07	0.002	0.94±0.08	0.92±0.09	0.90±0.07	0.04
BMI (kg/m ²)	32.86±7.14	29.55±7.35	28.27±6.93	0.002	33.21±7.53	28.59±6.79	28.38±6.69	0.001
Irisin (ng/ml) ^{b,c}	193.81±1.46	179.16±1.43	171.33±1.44	0.096	187.22±1.36	177.52±1.51	178.22±1.46	0.49
Leptin (ng/ml) ^{b,c}	16.86±2.95	15.20±3.46	13.47±3.33	0.34	18.41±2.87	13.90±3.48	12.93±3.35	0.14
CRP (mg/L) ^{b,c}	2.19±3.03	1.28±3.41	0.92±3.02	<0.001	2.09±3.37	1.26±3.23	0.83±2.73	<0.001
Fat mass (kg)	30.91±13.55	27.40±15.52	28.59±14.27	0.03	32.56±15.52	24.88±12.30	24.71±14.01	0.006
Fat mass (%)	31.38±9.57	30.73±28.25	28.26±11.25	0.16	32.76±10.72	28.92±11.51	28.18±10.45	0.04
Fat-free mass (kg)	65.25±13.70	58.46±13.90	57.86±11.89	0.006	63.83±13.54	57.86±13.73	59.69±12.57	0.10
Fat-free mass (%)	68.97±10.38	69.26±12.19	71.75±11.26	0.22	67.24±10.72	71.4±12.05	71.82±10.45	0.04
Abdominal circumference (cm)	106.49±15.84	99.73±18.13	94.32±16.27	<0.001	106.87±16.02	96.78±17.11	95.71±17.22	0.001
Total energy intake (kcal/d) ^d	1482.8±1.72	2002.4±1.73	2092.7±1.64	0.001	1507.6±1.78	1924.3±1.64	2279.7±1.64	<0.001
Energy from fat (%)	37.49±6.30	35.64±4.70	35.73±6.25	0.13	36.92±6.15	36.31±5.77	35.36±5.40	0.21
Energy from protein (%)	14.96±3.39	15.45±2.89	15.74±3.52	0.24	15.33±3.68	15.23±2.91	15.67±3.21	0.65
Energy from carbohydrate (%)	46.67±8.59	48.39±7.64	48.97±6.5	0.14	46.87±8.64	48.74±7.46	48.57±6.79	0.26

Abbreviation: AHEI, Alternate Healthy Eating Index; aMED, alternate Mediterranean Dietary Score.

Ranges of scores by tertile are 18.2–40.7, 40.8–49.3, and 49.4–76.1 for AHEI, and 0–3, 4–5, and 6–9 for aMED across each tertile groups.

^a P values are from linear regressions.

Data are mean ± S.D (all such values).

^b Log-transformed values were used for comparison.

^c The number of subjects with missing values for irisin, leptin, and CRP were 3, 2, and 2, respectively.

Table 4

Multivariate adjusted geometric means of biomarkers studied by tertiles (T) of AHEI and aMED scores

	AHEI				aMED			
	T1	T2	T3	P for trend ^a	T1	T2	T3	P for trend ^a
Irisin (ng/ml)								
Model 1 ^b	n=49 193.83±1.05	n=50 179.11±1.05	n=49 172.23±1.05	0.10	n=54 187.16±1.05	n=55 177.51±1.05	n=39 178.22±1.06	0.49
Model 2 ^c	190.38±1.05	180.55±1.05	172.95±1.05	0.20	185.49±1.05	179.47±1.05	177.68±1.06	0.56
Model 3 ^d	186.79±1.05	181.27±1.05	175.74±1.05	0.42	181.09±1.05	181.64±1.05	180.55±1.06	0.98
Model 4 ^e	187.54±1.05	179.29±1.05	176.80±1.05	0.43	184.04±1.05	179.83±1.05	180.73±1.06	0.85
Model 5 ^f	185.86±1.05	180.37±1.05	177.33±1.05	0.54	180.55±1.05	181.09±1.05	182.00±1.06	0.91
Model 6 ^g	188.29±1.05	180.05±1.05	176.62±1.05	0.40	182.0±1.05	180.73±1.04	182.91±1.06	0.95
CRP (mg/L)								
Model 1 ^b	n=49 2.30±1.18	n=50 1.25±1.17	n=50 0.89±1.17	<0.001	n=55 2.11±1.16	n=55 1.27±1.16	n=39 0.82±1.20	<0.001
Model 2 ^c	2.24±1.18	1.26±1.17	0.91±1.17	<0.001	2.07±1.16	1.29±1.16	0.82±1.20	<0.001
Model 3 ^d	1.81±1.16	1.31±1.15	1.08±1.15	0.02	1.65±1.15	1.45±1.14	0.96±1.17	0.02
Model 4 ^e	1.98±1.16	1.24±1.16	1.04±1.16	0.003	1.87±1.15	1.33±1.15	0.91±1.18	0.001
Model 5 ^f	1.81±1.15	1.25±1.15	1.13±1.15	0.02	1.68±1.14	1.39±1.14	1.00±1.17	0.02
Model 6 ^g	1.75±1.16	1.31±1.15	1.06±1.15	0.02	1.63±1.15	1.40±1.14	0.97±1.17	0.02
Leptin (ng/ml)								
Model 1 ^b	n=49 18.78±1.17	n=50 14.41±1.17	n=50 12.77±1.17	0.08	n=54 18.80±1.16	n=56 13.97±1.16	n=39 12.47±1.19	0.06
Model 2 ^c	18.10±1.17	14.72±1.17	12.97±1.17	0.14	18.45±1.16	14.30±1.15	12.38±1.19	0.08
Model 3 ^d	15.04±1.15	15.27±1.15	14.98±1.15	0.98	15.07±1.14	15.71±1.14	14.31±1.17	0.82
Model 4 ^e	17.01±1.17	14.25±1.16	14.23±1.16	0.42	17.55±1.16	14.44±1.15	13.09±1.18	0.18
Model 5 ^f	15.07±1.15	14.56±1.14	15.69±1.15	0.84	15.35±1.14	15.20±1.14	14.63±1.17	0.82
Model 6 ^g	14.73±1.15	15.29±1.14	15.58±1.15	0.78	15.32±1.14	15.58±1.14	14.53±1.17	0.82

Abbreviation: AHEI, Alternate Healthy Eating Index; aMED, alternate Mediterranean Dietary Score.

Ranges of scores by tertile of each biomarker are 18.2–40.7, 40.8–49.2, and 49.3–76.1 for AHEI, and 0–3, 4–5, and 6–9 for aMED across each tertile groups.

Data are expressed as geometric mean ± SE (all such values).

^a *P* values are from multiple linear regressions.

^b Model 1 was adjusted for gender.

^c Model 2: Model 1 + adjustment for age and race (Caucasian and African American)

^d Model 3: Model 2 + adjustment for BMI.

^e Model 4: Model 2 + adjustment for WHR.

^f Model 5: Model 2 + adjustment for percentage of body fat.

^g Model 6: Model 3 + adjustment for other mutual biomarkers.

Table 5

β regression coefficients for the relationships between dietary quality scores and log-transformed biomarkers

	Log-Irisin (ng/ml)				Log-Leptin (ng/ml)				Log-CRP (mg/L)			
	β	S.E.	Standardized β	p^a	β	S.E.	Standardized β	p^a	β	S.E.	Standardized β	p^a
AHEI												
Model 1 ^b	-0.004	0.002	-0.12	0.14	-0.01	0.008	-0.13	0.11	-0.03	0.008	-0.32	<0.001
Model 2 ^c	-0.004	0.003	-0.12	0.15	-0.02	0.007	-0.18	0.02	-0.03	0.008	-0.34	<0.001
Model 3 ^d	-0.003	0.002	-0.09	0.27	-0.02	0.007	-0.16	0.04	-0.03	0.008	-0.33	<0.001
Model 4 ^e	-0.002	0.003	-0.05	0.54	-0.004	0.007	-0.05	0.52	-0.02	0.007	-0.21	0.004
Model 5 ^f	-0.001	0.003	-0.04	0.61	-0.003	0.007	-0.03	0.64	-0.02	0.007	-0.19	0.008
aMDS												
Model 1 ^b	-0.008	0.02	-0.05	0.58	-0.06	0.05	-0.11	0.18	-0.18	0.05	-0.31	<0.001
Model 2 ^c	-0.008	0.02	-0.05	0.58	-0.08	0.04	-0.14	0.08	-0.18	0.04	-0.32	<0.001
Model 3 ^d	-0.004	0.01	-0.02	0.77	-0.07	0.04	-0.12	0.11	-0.18	0.04	-0.31	<0.001
Model 4 ^e	0.005	0.02	0.03	0.75	0.006	0.04	0.01	0.88	-0.10	0.04	-0.17	0.02
Model 5 ^f	0.004	0.02	0.02	0.78	0.001	0.04	0.002	0.98	-0.10	0.04	-0.17	0.02

Abbreviation: AHEI, Alternate Healthy Eating Index; aMDS, alternate Mediterranean Dietary Score.

^a P values are from multiple linear regressions.

^b Model 1: unadjusted

^c Model 2: adjusted for gender and age

^d Model 3: Model 2 + race

^e Model 4: Model 3 + BMI

^f Model 5: Model 4 + mutually for all other biomarkers (irisin, leptin, and CRP)