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Dietary Fiber Linked to Decreased Inflammation in Overweight Minority Youth

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Dietary Fiber Linked to Decreased Inflammation in Overweight Minority Youth

by

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Dedication

This thesis is dedicated to my parents, Connie and Frank Miller, and my partner in crime, Tyson Ferguson, for their unwavering support and dedication to my educational endeavors.

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Abstract

Dietary Fiber Linked to Decreased Inflammation in Overweight Minority Youth

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The University of Texas at Austin, 2015

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Objective: To examine the relationship between diet and inflammation, and adiposity in minority youth.

Design and Methods: A cross-sectional analysis of 142 overweight ($\geq 85^{th}$ BMI percentile) Hispanic and African American adolescents (14-18 y) with the following measures: anthropometrics, adiposity via magnetic resonance imagine (MRI), dietary intake via 24-hour dietary recalls, and inflammation markers from fasting blood draws utilizing a multiplex panel. Partial correlations were estimated and ANCOVA models fit to examine the relationship between dietary variables, inflammation markers, and adiposity measures with the following *a priori* covariates: Tanner stage, ethnicity, sex, total energy intake, total body fat, and total lean mass.

Results: Inference based on ANCOVA models showed that the highest tertile of fiber intake (mean intake of 21.3 ± 6.1 g/d) versus the lowest tertile of fiber intake (mean intake of 7.4 ± 1.8 g/d) was associated with 36% lower plasminogen activator inhibitor-1 (PAI-1) ($P = 0.02$) and 43% lower resistin ($P = 0.02$), independent of covariates. Similar

results were seen for insoluble fiber. No other dietary variables included in this study were associated with inflammation markers.

Conclusions: These results suggest that increases in dietary fiber could play an important role in lowering inflammation and therefore metabolic disease risk in high-risk minority youth.

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Introduction[1]

Estimates from the National Health and Nutrition Examination Survey (NHANES) show that 20.5% of adolescents (12-19 y) were classified as obese (BMI ≥ 95th percentile) in 2011-2012 (1). This problem is exacerbated in the Hispanic and African American populations; with 22.6% of Hispanic and 22.1% of African American adolescents being classified as obese, compared to only 19.6% of non-Hispanic white (NHW) youth (1). Obesity in childhood and adolescence is particularly troubling as it is associated with the development of risk factors for cardiovascular disease and type 2 diabetes (2).

Inflammation is one of the leading contributors to the development of metabolic disease and cardiovascular complications, and unsurprisingly, obesity is now considered a chronic inflammatory disease. Adipose tissue was previously thought of as an inert storage organ, but research has shown that excess adipose tissue associated with obesity contributes to the release of pro-inflammatory cytokines such as resistin and plasminogen activator inhibitor-1 (PAI-1). (3). Obese individuals have higher levels of inflammatory markers, with greater rates found in both Hispanic and African American populations (4). This relationship between inflammation and obesity has been noted in children as young as six years of age (5).

Diet is a critical factor that contributes to both obesity and metabolic disease. Consumption of added sugars has risen steadily in the U.S., and it has been hypothesized that regular consumption of refined carbohydrates may increase the risk for obesity and metabolic disease (6, 7). These results have also been seen in minority populations, with

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[1] Portions of this paper have been previously published as Miller et al. Dietary Fibre Linked to Decreased Inflammation in Overweight Minority Youth. *Pediatr Obes* 2015.

added sugar positively associated with total fat mass and negatively associated with insulin secretion and β-cell function in Hispanic children (8, 9). Dietary fiber has been shown to aid in the prevention of childhood obesity and development of metabolic disease (10, 11). Previous studies in overweight Hispanic children have found an inverse relationship between dietary fiber and adiposity measures, such as waist circumference, visceral adipose tissue (VAT), and BMI, as well as metabolic syndrome (12, 13). However, further investigation exploring the interrelationships between diet, inflammation, and adiposity are warranted with the intent to better inform obesity intervention work.

To date, few studies have looked at the relationship between diet, inflammation, and adiposity in youth or minority populations. The purpose of these analyses was to examine the relationship between diet and inflammation, and the contribution of adiposity to this relationship, in overweight and obese Hispanic and African American adolescents. We hypothesized that a healthier diet profile (i.e. one high in fiber and low in added sugar intake) will be related to lower inflammation and adiposity measures.

Subjects and Methods

SUBJECTS

This cross-sectional study utilized data from three studies conducted at the University of Southern California. These studies had identical data collection measures and methodology, and subjects were recruited from a variety of locales including health clinics, schools, community centers, and health fairs (14-16). Criteria for inclusion in these three studies are as follows: a) Hispanic or African American ethnicity (all four grandparents of Hispanic or African American origin) via self-report, b) enrolled in 9th-12th grade, c) BMI ≥85th percentile for age and sex based on guidelines from the Centers for Disease Control and Prevention (17), d) complete anthropometric data, at least one inflammatory marker, and at least two days of valid dietary data, e) no medications or conditions that affect metabolism or body composition, and f) no participation in a nutrition, physical activity, or weight reduction program six months prior to data collection. The final sample included 142 African American and Hispanic adolescents (14-18 y) with complete metabolic and dietary data, and at least one inflammation marker. The Institutional Review Board of the University of Southern California (USC) approved all studies and informed permission and assent were obtained from both parents and adolescents.

PHYSICAL, METABOLIC, AND ADIPOSITY DATA

A licensed health care provider at USC Clinical Translational Unit performed a comprehensive medical history and physical examination on all participants. Tanner stage was determined using established guidelines (18, 19), and height and weight were measured to the nearest 0.1 cm and 0.1 kg using a wall-mounted stadiometer (Seca 240, Chino, CA) and a beam medical scale (Health O Meter Professional ProPlus, Bedford

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Heights, OH), and the average of two measures was used for analysis. BMI and BMI z-scores were determined using Epi Info (Centers for Disease Control and Prevention, Atlanta, GA). Total body fat and total lean mass were measured by dual-energy X-ray absorptiometry (Hologic QDR 4500W, Bedford, MA). Abdominal fat distribution, subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and hepatic fat fraction (HFF) were determined using Magnetic Resonance Imaging (MRI) on a 1.5-Tesla or 3.0-Tesla machine (General Electric Healthcare, Waukesha WI) at the USC imaging center, as described previously (20, 21).

DIETARY DATA

Dietary intake was assessed through multiple 24-hour dietary recalls using the multiple pass technique. Recalls were done in person or over the phone by research staff that were trained and supervised by a Registered Dietitian. Dietary data were analyzed with the Nutrition Data System for Research software (NDS-R, 2009, Minneapolis MN). The program was used to calculate key dietary variables included in the analysis: total energy, carbohydrates, protein, fat, total fiber, insoluble fiber, soluble fiber, total sugar, added sugar, servings of dark-green/deep-yellow vegetables, legumes, vegetables excluding white potatoes and fried vegetables, fruit excluding juice, sugar-sweetened beverages, and sweet desserts. The Willett exclusion criteria was used to remove subjects with improbable caloric intake, which resulted in two subjects being excluded (22).

INFLAMMATION MARKERS

Plasma was obtained from the participants via a frequently sampled intravenous glucose tolerance test (12, 23, 24). Interleukin-6 (IL-6), Interleukin-8 (IL-8), leptin, adiponectin, hepatocyte growth factor (HGF), nerve growth factor (NGF), PAI-1, monocyte chemoattractant protein-1 (MCP-1), resistin, and tumor necrosis factor- α

(TNF-α) were chosen based on their relevance to obesity, liver fat, and related metabolic disease (3, 25). Inflammatory markers were obtained from subjects that had available plasma (n=142) and were assayed in duplicate using the Millipore Multiplex MAP technology (Millipore, Billerica, MD). Fourteen subjects had undetectable values and were removed from the dataset, which lead to differences in the number of inflammatory markers for each subject. However, participants with undetectable inflammation values compared to those with detectable values did not differ in dietary intake (i.e, fiber and energy intake) and demographics (i.e., sex, ethnicity, age, and Tanner).

STATISTICAL ANALYSES

Prior to analyses, the data were checked for normality and variables were natural log (IL-6, IL-8, adiponectin, HGF, NGF, MCP-1, PAI-1, resistin, TNF-α, HFF, and SAT) or square root (leptin and VAT) transformed. Untransformed means are provided in the tables and text, for ease of interpretation. Partial correlations were performed between all dietary variables, inflammatory markers and adiposity measures. The following *a priori* covariates were used: sex, ethnicity, Tanner stage, energy intake, total body fat, VAT (for correlations with SAT and HFF), SAT (for correlations with VAT), and total lean mass. Dietary variables that were significantly correlated to inflammatory markers or adiposity measures were then divided into tertiles. ANCOVA was performed with the Bonferroni post-hoc test to further assess the relationship between tertiles of dietary variables and adiposity and inflammatory markers. The same covariates listed above were used in the ANCOVA analyses. All analyses were performed with SPSS version 21 (SPSS, Chicago, IL). Significance was set at $P \leq 0.05$.

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Results

Two hundred and thirteen participants living in Los Angeles were prescreened and consented for the three studies included in these analyses. Of those 213, 163 participants completed dietary, metabolic, and anthropometric measures and 142 participants had inflammation data. Analyses were conducted on 142 overweight and obese Hispanic and African American youth (14-18 y) who had complete and plausible dietary and anthropometric data, and at least one inflammation parameter (**Table 1**). Partial correlations between fiber intake, inflammation markers, and adiposity measures are shown in **Table 2.** After controlling for covariates, total fiber intake was inversely related to both PAI-1 and resistin levels (r = -0.22, P = 0.01; r = -0.25, P < 0.01, respectively), and insoluble fiber intake was inversely related to PAI-1 and resistin levels (r = -0.27, P < 0.01; r = -0.28, P < 0.01 respectively). Contrarily, insoluble fiber intake was positively correlated to MCP-1 (r = 0.20, P = 0.03). No other dietary variables were significantly correlated with inflammation markers.

There were no significant correlations between dietary variables and adiposity measures, however adiposity measures were significantly associated with several inflammation markers. VAT was negatively correlated to adiponectin (r = -0.20, P = 0.05) and positively correlated to IL-8 and PAI-1 (r = 0.19, P = 0.05; r = 0.18, P = 0.05, respectively), and SAT was positively associated with leptin and PAI-1 (r = 0.22, P = 0.03; r = 0.20, P = 0.03), and negatively associated with TNF-α (r = -0.28, P < 0.01, respectively) after controlling for covariates. There were no significant correlations between HFF and inflammation markers.

Analysis of covariance models were fit to examine the differences in inflammation between tertiles of total and insoluble fiber intake (**Table 3**). Participants

who consumed the greatest amount of total fiber had 36% lower levels of PAI-1 ($P =$ 0.02) and 43% lower levels of resistin ($P = 0.02$) compared to those with the lowest fiber intake, independent of covariates. Findings for insoluble fiber expressed in tertiles were consistent with those for total fiber, with high intakes of insoluble fiber (mean intake of 14.8 ± 4.2 g/d) being linked to 36% lower levels of PAI-1 ($P = 0.02$) and 44% lower levels of resistin ($P < 0.01$) compared to those with the lowest insoluble fiber intake (mean intake of 4.6 ± 1.2 g/d), independent of covariates (data not shown). ANCOVA models also showed a significant difference among tertiles of insoluble fiber and MCP-1 levels; with high intakes of insoluble fiber linked to 25% higher levels of MCP-1 ($P =$ 0.02) when compared to medium intakes of insoluble fiber (mean intake of 9.1 ± 1.1 g/d). Ethnicity was significant in the models, however the interactions between ethnicity and fiber variables were not significant and therefore the results are presented with the full sample and ethnicity is controlled for in all models.

Discussion

As hypothesized, high dietary fiber intake was linked to decreased inflammation. Specifically, total and insoluble fibers were inversely correlated with PAI-1 and resistin. Insoluble fiber was also positively correlated with MCP-1. Studies have shown resistin to be important in the development of hepatic insulin resistance, and PAI-1 is associated with thrombosis and the development of insulin resistance (26, 27). The levels of PAI-1 and resistin seen in these individuals are higher than levels seen in other studies performed in children and adolescents (28-30). However, these previous studies included normal weight subjects and/or Caucasian ethnicities from other countries. There were no significant associations between dietary variables and adiposity measures, however, both VAT and SAT were significantly correlated with inflammatory markers. VAT was negatively associated with adiponectin, and positively associated with IL-8 and PAI-1. SAT was positively associated with leptin and PAI-1, and negatively associated with TNF-α. There were no significant correlations between HFF and any inflammation markers.

Few studies have examined the relationship between diet, inflammation, and adiposity in adults, and even fewer have examined the relationship in high-risk minority youth. Previous studies have found negative correlations between both total fiber and fruit and vegetable intake, and various inflammation markers. In a cross-sectional study of 559 normal weight African American and Caucasian adolescents (14-18 y) by Parikh et al., total fiber intake was negatively associated with C-reactive protein (CRP), fibrinogen, and VAT, and was positively associated with adiponectin, independent of covariates (28). However, the study by Parikh et al. did not find an association between total fiber intake and resistin, included mostly normal weight participants, and did not

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examine soluble versus insoluble fiber intake. Our study did not assay CRP or fibrinogen, however we did include a thorough panel of other obesity-related inflammatory markers. Another study by Hermsdorff et al. involving 120 healthy, normal weight, Spanish young adults (18-30 y, BMI 18.5-30.5 kg/m^2), found that fiber intake from fruits and vegetables was associated with lower plasma levels of CRP, homocysteine, TNF- α and lower levels of intercellular adhesion molecule 1 (ICAM1), TNF-α, and NFκB1 gene expression in peripheral blood mononuclear cells (31). However, this study was conducted in Spanish young adults living in Spain who have dramatically different metabolic risk factors and environments compared to Mexican-Americans living in Los Angeles. The study by Hermsdorff et al. also did not examine the relationship between fiber and plasma PAI-1 or resistin levels and utilized food-frequency questionnaires, whereas our study, along with the study from Parikh et al., utilized multiple 24-hour recalls. A cross-sectional study in 445 Hispanic and NHW adults (≥ 60 y) found a negative correlation between fruit and vegetable intake and CRP and homocysteine levels (32), and another cross-sectional study of 1200 Puerto Rican adults (45-75 y) found that variety, not quantity of fruits and vegetables, was associated with lower levels of CRP (33). The previous studies by Parikh and Hermsdorff have elucidated the relationship between dietary fiber intake and lower levels of inflammation markers in Caucasian and African American normal weight adolescents, as well as Spanish normal weight adults (28, 31). This is the first study to examine the relationship between dietary fiber intake and inflammation in primarily obese Hispanic and African American adolescents.

No other dietary variables were linked with inflammation markers in this study. This may be due, in part, to the fact that the correlations between total and insoluble fiber and PAI-1 and resistin, while significant, are fairly small. Breaking down total and insoluble fiber into individual food groups attenuates the significant correlation.

However, the top five sources of fiber in this population include non-citrus fruit, vegetables in mixed dishes, whole grain tortillas, tomatoes and legumes. These findings would suggest that instead of focusing on one specific food, inflammation could be lowered through eating more fiber-rich foods in general. The Dietary Reference Intakes for Americans ages 9-18 are 26-38 g/d (34). Results from NHANES between 2001 and 2002 show that children (9-18 y) consumed an average of 12-15 g/d, which is about half of the recommended amount for fiber (35). Our data is in line with the national findings, with the average intake well below the recommendations (mean intake of 14 g/d). In our analyses, the difference in fiber consumption between the first and third tertiles was 14 g/d, equivalent to about 1 cup of pinto beans. Therefore, our data suggest that increases in fiber consumption that are more in line with the recommendations could play an important role in lowering inflammation and therefore disease risk in high-risk minority youth.

Our previous longitudinal study of 85 overweight Hispanic children (11-17 y) found that increases in total and insoluble fiber intake were linked to decreases in VAT over two years, independent of covariates (36). Surprisingly, we did not see any relationship between dietary variables and adiposity measures. This may be due to the cross-sectional nature of this study and inclusion of both African American and Hispanic youth. As mentioned before, the cross-sectional study by Parikh et al. also found an inverse relationship between fiber intake and VAT, however this study included mostly normal weight Caucasian and African American adolescents (28). Interestingly, SAT was found to be negatively associated with TNF-α, which is the opposite direction of expected and there is no clear explanation for this finding. However, VAT has been shown to be the more metabolically active tissue (37), and therefore the relationship between VAT and inflammatory markers may be more meaningful. Our study includes

only overweight or obese participants, and it is possible that having a homogenous population could potentially mask an association between fiber and VAT. Although we did not see a relationship between fiber and VAT, we did see that adipose-associated inflammation markers, resistin and PAI-1, are negatively associated with fiber intake. It is possible that fiber intake is related to a decrease in expression of inflammation markers coming from VAT, without necessarily being associated with lower VAT levels. A potential biological mechanism involves the relationship between fiber and oxidized low-density lipoprotein. Dietary fiber, and specifically insoluble fiber, has been found to decrease oxidation of low-density lipoprotein, which may potentially reduce inflammatory mediators such as PAI-1 (38-40). Another possible mechanism involves modulation of the gut microbiota by dietary fiber. Gut microbiota have recently been shown to contribute to low-grade inflammation typically seen in obesity and other metabolic disease (41). Dietary fiber, and specifically insoluble fiber, is fermented by gut microbiota into short chain fatty acids. Recent studies have shown that short chain fatty acids produced by gut microbiota are capable of reducing inflammation (42). Therefore, dietary fiber could act on gut microbiota to decrease inflammation in a manner independent of VAT.

One limitation of this study is the cross-sectional design, and thus, causal relationships cannot be determined. A larger prospective study is warranted to further investigate these associations. A limitation of this study is that this study included mostly obese individuals compared to overweight individuals. When the sample was split into obese versus overweight participants, the significant results remained in the obese individuals (n=117) but were attenuated in the overweight population (n=25). Because the overweight subsample is so small, these results are difficult to interpret and thus the entire population was analyzed as a whole. Another limitation is the issue of

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underreporting with 24-hour recalls, especially with an overweight/obese sample (43). However, our entire sample is overweight or obese and therefore with a homogenous population it is expected that there would be similar levels of underreporting throughout the sample. In addition, there were no significant differences in energy intake or fiber intake between overweight and obese individuals. The lower number of African-Americans in this study may be another limitation, however the interactions between ethnicity and fiber variables were not significant in the model, and therefore ethnicity was used as a covariate in all analyses. Finally, although at least one inflammatory marker was obtained from 142 subjects, not all inflammatory markers were available for each participant, as some subjects had undetectable values.

These results show that fiber intake, particularly insoluble fiber, is associated with lower levels of detrimental inflammatory markers in overweight minority youth. Given that adolescents are consuming well below the recommended amounts of fiber, these findings are especially important. Increasing total fiber intake to be more in line with current recommendations could lead to lower levels of inflammation and therefore decrease metabolic disease risk in African American and Hispanic youth. Examining the impact of future interventions targeting increased dietary fiber on inflammation markers and adiposity is warranted, particularly in high-risk youth.

Table 1: Characteristics of the sample [1,16]

Physical Characteristics [2]	Value
Sex (M/F)	47/95
Age (y)	15.3 ±0.1
Ethnicity (African American/Hispanic)	53/89
Tanner (%)	
1	0.7
2	2.1
3	6.3
4	23.2
5	67.6
Height (cm)	164.1 ±8.2
Weight (kg)	93.5 ±22.7
BMI percentile	97.3 ±0.3
BMI z score	2.1 ±0.0
Total fat (kg)	35.5 ±1.1
Total lean (kg)	52.5 ±0.8
Adiposity Measures	
SAT (L) [3]	12.2 ±0.5
VAT (L) [3]	1.5 ±0.1
HFF (%) [4]	5.1
Inflammatory Markers	
IL-8 (pg/mL) [6]	3.0 ±0.2
Leptin (ng/mL) [7]	53.1 ±2.7
TNF-α (pg/mL) [8]	9.7 ±0.6
MCP-1 (pg/mL) [2]	230.3 ±9.9
HGF (ng/mL) [9]	1.1 ±0.1
NGF (pg/mL) [10]	11.2 ±0.9
Adiponectin (μg/mL) [11]	18.8 ±0.9
PAI-1 (ng/mL) [2]	124.4 ±8.0
Resistin (ng/mL) [12]	37.5 ±2.2
Dietary Characteristics [2]	
Total energy (kcal/d)	1840.8 ±51.1
Carbohydrates (g/d)	236.1 ±7.8
Protein (g/d)	69.2 ±2.0
Fat (g/d)	71.2 ±2.3
Total fiber (g/d)	14.0 ±0.6
Soluble fiber (g/d)	4.2 ±0.2
Insoluble fiber (g/d)	9.5 ±0.4
Total sugar (g/d)	109.6 ±4.8
Added sugar (g/d)	75.0 ±4.0
Food Servings (servings/d) [2]	
Dark-green, deep-yellow vegetables	0.2 ±0.5
Legumes	0.3 ±0.5
All vegetables [13]	1.4 ±1.0
All fruit [14]	0.7 ±0.9
Whole grains	0.9 ±1.1
Refined grains	4.5 ±2.2
Sugar sweetened beverages [15]	1.6 ±1.4
Sweet desserts	2.1 ±3.5

[1] All values are mean ± SE
Sample sizes: [2] n=142; [3] n=127; [4] n=111; [6] n=129; [7] n=124; [8] n=141; [9] n=140;
[10] n=114; [11] n=120; [12] n=123
[13] Excluding potatoes and fried vegetables
[14] Excluding 100% juice
[15] Excluding 100% juice and flavored milk.
[16] Hepatic Fat Fraction = HFF; Hepatocyte Growth Factor=HGF; Interleukin-6=IL-6; Interleukin-8=IL-8; Monocyte Chemoattractant Protein-1=MCP-1; Nerve Growth Factor=NGF; Plasminogen Activator Inhibitor-1=PAI-1Tumor Necrosis Factor-α=TNF-α

Table 2: Associations Between Total Fiber Intake, Adiposity, and Inflammation Markers

	Total Fiber (g/d) [1]	*P* value	Insoluble Fiber (g/d) [1]	*P* value	VAT [2]	*P* value	SAT [2]	*P* value	HFF [2]	*P* value
IL-8 (pg/mL)	<0.01	0.94	0.04	0.68	0.19	0.05	-0.09	0.37	-0.13	0.23
Leptin (ng/mL)	0.03	0.75	0.04	0.72	0.17	0.09	0.22	0.03	-0.07	0.51
Adiponectin (μg/mL)	-0.14	0.16	-0.13	0.18	-0.20	0.05	0.17	0.11	-0.10	0.36
TNF-α (pg/mL)	0.03	0.77	0.07	0.43	0.16	0.09	-0.28	<0.01	0.09	0.37
MCP-1 (pg/mL)	0.17	0.06	0.20	0.03	0.07	0.44	-0.13	0.18	0.11	0.29
HGF (ng/mL)	0.01	0.90	0.03	0.77	-0.09	0.37	-0.16	0.08	-0.11	0.26
NGF (pg/mL)	0.03	0.77	0.05	0.65	0.10	0.35	<0.01	0.98	0.04	0.71
PAI-1 (ng/mL)	-0.22	0.01	-0.27	<0.01	0.18	0.05	0.20	0.03	0.03	0.77
Resistin (ng/mL)	-0.25	<0.01	-0.28	<0.01	0.02	0.83	0.10	0.35	0.04	0.70

[1] Correlations are adjusted for sex, ethnicity, energy intake, Tanner stage, total body fat, and total lean mass

[2] Correlations are adjusted for sex, ethnicity, energy intake, Tanner stage, and VAT or SAT, and total lean mass

[3] Hepatic Fat Fraction = HFF; Hepatocyte Growth Factor=HGF; Interleukin-6=IL-6; Interleukin-8=IL-8; Monocyte Chemoattractant Protein-1=MCP-1; Nerve Growth Factor=NGF; Plasminogen Activator Inhibitor-1=PAI-1; Subcutaneous adipose tissue=SAT; Tumor Necrosis Factor-α=TNF-α; Visceral adipose tissue=VAT

Significance is set at $P \leq 0.05$

Table reflects Pearson's r values.

Table 3: Physical, Adiposity, Inflammation, and Dietary Characteristics by Tertiles of
Total Fiber

Total Fiber (g/d)	Tertile 1	Tertile 2	Tertile 3	*P* value
Mean intake (g/d)	7.4 ±1.8	13.3 ±1.2	21.3 ±6.1	
Physical Characteristics [3]				
Sex (F) [4]	33	29	33	0.64
Age (y)	15.0 ±0.2	15.1 ±0.2	15.5 ±0.2	0.24
Ethnicity (African American/Hispanic) [4]	24/23	14/33	15/33	0.06
BMI z score	2.1 ±0.0	2.1 ±0.0	2.1 ±0.0	0.69
Total fat (kg) [5]	35.0 ±1.7	33.9 ±1.5	35.1 ±1.6	0.91
Total lean (kg) [6]	53.6 ±1.4	51.7 ±1.2	50.1 ±1.3	0.47
Adiposity Measures				
SAT [7,8]	11.8 ±0.7	11.5 ±0.7	12.8 ±0.7	0.42
VAT [7,9]	1.5 ±0.1	1.5 ±0.1	1.4 ±0.1	0.68
HFF (%) [8,10]	4.8 ±0.4	5.2 ±0.4	4.9 ±0.4	0.89
Inflammatory Markers				
IL-8 (pg/mL) [11]	3.1 ±0.4	2.7 ±0.4	3.4 ±0.4	0.67
Leptin (ng/mL) [12]	51.6 ±4.8	53.7 ±4.3	53.0 ±4.6	0.96
TNF-α (pg/mL) [13]	9.6 ±1.2	9.6 ±1.0	10.3 ±1.1	0.94
MCP-1 (pg/mL) [3]	215.3 ±19.8	221.5 ±17.4	243.0 ±18.4	0.45
HGF (ng/mL) [14]	1.1 ±0.1	1.1 ±0.1	1.0 ±0.1	0.87
NGF (pg/mL) [15]	18.0 ±3.2	13.7 ±2.9	10.2 ±3.2	0.59
Adiponectin (µg/mL) [16]	20.2 ±1.8	19.1 ±1.6	18.6 ±1.7	0.93
PAI-1 (ng/mL) [3]	154.5 ±14.3	125.8 ±12.6	98.2 ±13.3	**T1vs.T3, 0.02**
Resistin (ng/mL) [17]	46.9 ±4.1	39.6 ±3.7	26.9 ±3.8	**T1vs.T3, 0.02**
Dietary Characteristics [3]				
Total energy (kcal/d) [18]	1595.8 ±43.7	1837.0 ±41.8	2008.8 ±41.8	**T1vs.T2, <0.01; T1vs.T3, <0.01; T2vs.T3, 0.05**
Carbohydrates (g/d)	208.6 ±7.5	235.2 ±6.6	253.9 ±6.9	**T1vs.T2; T1vs.T3, <0.01**
Protein (g/d)	72.1 ±2.9	66.1 ±2.5	67.9 ±2.7	0.33
Fat (g/d)	78.5 ±2.4	67.6 ±2.1	64.5 ±2.2	**T1vs.T2; T1vs.T3, <0.01**
Soluble fiber (g/d)	3.0 ±0.2	3.7 ±0.2	5.9 ±0.2	**T1vs.T2vs.T3, <0.01**
Insoluble fiber (g/d)	5.5 ±0.5	9.2 ±0.4	14.0 ±0.4	**T1vs.T2vs.T3, <0.01**
Total sugar (g/d)	98.2 ±6.7	116.2 ±5.9	106.7 ±6.2	0.14
Added sugar (g/d)	76.0 ±6.1	78.8 ±5.3	63.0 ±5.7	0.19

[1] All values are mean ± SE
[2] *A priori* covariates: ethnicity, energy intake, total body fat, and total lean mass
Sample sizes: [3] n=142; [7] n=127; [10] n=111; [11] n=129; [12] n=124; [13] n=141;
[14] n=140; [15] n=114; [16] n=120; [17] n=123
[4] Chi-squared analysis
[5] Comparisons adjusted for: ethnicity, energy intake, and total lean mass
[6] Comparisons adjusted for: ethnicity, energy intake, and total body fat
[8] Comparisons adjusted for: ethnicity, energy intake, VAT, and total lean mass
[9] Comparisons adjusted for: ethnicity, energy intake, SAT, and total lean
[18] Comparisons adjusted for: ethnicity, non-carbohydrate energy intake, total body fat, and total lean mass

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