Physical Fitness but Not Diet Quality Distinguishes Lean and Normal Weight Obese Adults

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ABSTRACT

Background Individuals with normal weight obesity (NWO) have increased cardiometabolic disease and mortality risk, but factors contributing to NWO development are unknown.

Objective The objective of this study was to determine whether diet quality scores and physical fitness levels differed between adults classified as lean, NWO, and overweight-obese. Secondary objectives of the study were to compare clinical biomarkers and food groups and macronutrient intakes between the three groups, and to test for associations between body composition components with diet quality scores and physical fitness levels.

Design This is a secondary data analysis from a cross-sectional study that included metropolitan university and health care system employees. Body composition was measured by dual energy x-ray absorptiometry. Individuals with a body mass index <25 kg/m^2 and body fat $>23\%$ for men and $>30\%$ for women were classified as having NWO. Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension score, and Mediterranean Diet Score were calculated from Block food frequency questionnaires. Physical fitness was assessed by measuring maximal oxygen uptake (VO_2 maximum) during treadmill testing.

Participants/setting This study included 693 adults (65% women, mean age 48.9 $\pm$ 11.5 years) enrolled between 2007 and 2013 in Atlanta, GA.

Main outcome measures The main outcome measures were Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension, and Mediterranean Diet Score diet quality scores and maximal oxygen uptake.

Statistical analyses Multiple linear regression analyses with post hoc comparisons were used to investigate group differences in fitness, diet quality, and biomarkers. Regression analyses were also used to examine relationships between diet quality scores and fitness with body composition.

Results VO_2 maximum was significantly lower in the NWO compared with the lean group (36.2 $\pm$ 0.8 mL/min/kg vs 40.2 $\pm$ 1.0 mL/min/kg; $P < 0.05$). Individuals with NWO reported similar diet quality to lean individuals and more favorable Alternate Healthy Eating Index and Dietary Approaches to Stop Hypertension scores than individuals with overweight-obesity ($P < 0.05$). Diet quality scores and physical fitness levels were inversely associated with percent body fat and visceral adipose tissue ($P < 0.05$), regardless of weight status. Individuals with NWO exhibited higher fasting blood insulin concentrations, insulin resistance, low-density lipoprotein cholesterol, and triglyceride levels, and significantly lower high-density lipoprotein cholesterol levels than lean individuals ($P < 0.05$).

Conclusions Physical fitness was significantly decreased in individuals with NWO compared with lean individuals. Higher diet quality was associated with decreased total and visceral fat but did not distinguish individuals with NWO from lean individuals.
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OBESITY IS A PRINCIPAL, PREVENTABLE RISK FACTOR for numerous well-characterized diseases such as cardiovascular disease, type 2 diabetes, and some cancers, which represent leading causes of death globally.[1,2] When examining associations with disease, obesity is typically assessed by body mass index (BMI) to identify at-risk individuals. Although BMI is an important measure used for epidemiology surveillance, clinical

observations reveal that individuals classified as normal weight or obese using BMI may present with an unhealthy or healthy metabolic profile, respectively.[3,4] Thus, BMI does not capture the large heterogeneity in cardiometabolic risk observed across individuals. This is because BMI measurements do not differentiate between proportions of fat and fat-free mass that contribute to total body weight or indicate fat mass distribution, which are important drivers of metabolic disease development.[5,6] Further, BMI does not account for age, race, sex, or fitness level, which influence body composition.[7] Therefore, assessment of obesity and disease risk using BMI categories may misclassify individuals at risk for chronic disease.

Normal weight obesity (NWO) has emerged as a term to denote individuals who have a normal weight according to BMI guidelines but a disproportionately high body fat mass.[8] Studies have suggested the NWO body composition phenotype is associated with increased risk of chronic diseases and cardiometabolic abnormalities, including dyslipidemia, hypertension, glucose intolerance, and increased levels of inflammation and oxidative stress markers.[8-15] Further, individuals with NWO exhibit a higher mortality risk compared with their lean counterparts and metabolically healthy obese individuals.[8,13,16,17] Despite this increase in disease risk, individuals with NWO may be overlooked by health professionals and/or misclassified as healthy when solely utilizing BMI as a screening tool.[18]

Specific factors driving the prevalence of NWO are unknown. Lifestyle factors, such as diet quality and physical activity are important factors influencing health and disease. A higher quality diet, characterized by a greater consumption of vegetables, fruits, whole grains, healthy fats, and lean proteins, is associated with lower chronic disease and mortality risk.[19-23] A higher diet quality, assessed by indexes such as the Dietary Approaches to Stop Hypertension (DASH) diet score, Alternate Healthy Eating Index (AHEI), and Mediterranean Diet Score (MDS), is associated with improvements in blood pressure, lower biomarkers of inflammation and oxidative stress, and reduced risk for type 2 diabetes and cardiovascular disease.[19-28] In addition, physical inactivity is a major risk factor for chronic diseases and accounts for an estimated 9% of global premature mortality from leading cardiometabolic diseases.[29,30] Physical fitness is a measurable attribute that reflects an individual's ability to perform physical activity.[31] Knowledge is limited on the role of diet quality and physical fitness in individuals with NWO. The objective of this study was to examine diet quality scores and physical fitness levels between adults categorized into three body composition subtypes (lean, NWO, and overweight-obese). It was hypothesized that individuals with NWO would have similar diet quality scores and physical fitness levels as individuals with overweight-obesity and lower diet quality scores and physical fitness levels than lean participants. Given that lifestyle behaviors are key drivers of metabolic health and disease,[32] secondary aims of this study were to provide extensive dietary and metabolic phenotyping of individuals with NWO by comparing clinical biomarkers, markers of oxidative stress and inflammation, and food group and macronutrient intakes between the three groups. A final objective of the study was to test for associations between body composition components with diet quality scores and physical fitness levels.

RESEARCH SNAPSHOT

Research Question: Do diet quality scores and physical fitness levels differ between adults categorized as lean, as having normal weight obesity, or as having overweight-obesity? Also, do clinical biomarkers and food groups and macronutrient intakes differ between the three groups, and are body composition components associated with diet quality scores and physical fitness levels?

Key Findings: In a large cohort of working adults, participants with normal weight obesity had lower physical fitness levels than lean individuals but reported similar diet quality to lean participants and higher diet quality scores than participants with overweight-obesity. For clinical biomarkers, individuals with normal weight obesity and overweight-obesity exhibited overall worse metabolic panels compared with lean participants. Regardless of body composition group, higher physical fitness and diet quality was associated with lower total and visceral adiposity.

MATERIALS AND METHODS

Participants and Study Design

This cross-sectional study utilized the Emory-Georgia Tech Center for Health Discovery and Well Being Predictive Health Institute cohort (http://predictivehealth.emory.edu) based in Atlanta, GA. This is a secondary analysis of existing data. This cohort is composed of Emory University and Emory Healthcare employees who had been employed within the Emory system for at least 2 years. General exclusion criteria were having a poorly controlled chronic disease, acute illness, hospitalization within the previous year, and women who were pregnant or breastfeeding. From an alphabetized list of all eligible employees of Emory University and Emory Healthcare (approximately 30,000), every 10th employee was invited by e-mail to participate in the study. Of the approximately 3,000 invited employees who responded to the e-mail and underwent initial screening in the electronic medical record and then by telephone interview (when available), a total of 739 were ultimately deemed eligible and enrolled in the study. This final number was also influenced by the availability of funds at the time of cohort recruitment. The complete study protocol was previously described.[33,34] The study was approved by the Emory Institutional Review Board and all participants provided informed consent. Participants underwent extensive metabolic testing, including clinical laboratory analysis, dietary assessment, and exercise testing. Demographic information, educational attainment, and annual household income were self-reported. Participants were categorized as having a history of chronic disease (eg, hypertension, hyperlipidemia, or diabetes mellitus) in the case that they reported a past or current diagnosis or were currently taking medications to treat hypertension, hyperlipidemia, or diabetes mellitus. Only participants with available body composition and anthropometric data were included in this analysis (n = 693).

Body Composition Analysis and Body Composition Subgroups

Body composition, including visceral adipose tissue (VAT), was assessed by dual energy x-ray absorptiometry using a Lunar iDXA densitometer with CoreScan™ software (GE Healthcare). A single measure of height and weight were taken in light clothing without shoes using a digital scale and stadiometer (Tanita TBF-25; Tanita Health Management). Height was recorded to the nearest eighth of an inch, weight was recorded to the nearest 10th of a pound, and both measures were converted to metric units. BMI was calculated as body weight in kilograms divided by height in meters squared. Participants were categorized as either lean, NWO, or overweight-obese based on BMI and sex-specific body fat percent cut points. A body fat percent >23 was considered elevated for males, and a body fat percent >30 was considered elevated for women based on previously published literature.[35] Lean participants had a BMI value between 18.5 and 24.9 and a body fat percent below the sex-specific cutoff values. NWO was characterized as a BMI between 18.5 and 24.9 and a body fat percent above the sex-specific cutoff values. Participants with overweight-obesity had a BMI ≥25 and a body fat percent above the sex-specific cutoff values. A health professional trained in anthropometry assessed waist circumference (WC) to the closest millimeter using a tape measure. Three WC measurements were taken at the umbilicus, and the average value is reported.

Diet Quality Scores, Dietary Food Groups, and Macronutrients

Diet quality scores were calculated from dietary intake data assessed using 2005 Block food frequency questionnaires (NutritionQuest), which reflected dietary intake over the past year.[36-38] Reported intakes that were <500 kcal/day or >5,000 kcal/day were considered implausible values and excluded. All dietary data were energy adjusted per 1,000 kcal. Three diet quality scores were calculated as previously described within this cohort:[24] AHEI[28], DASH[39] with adapted scoring of the sweets component,[25,40] and MDS.[41] The AHEI ranges from 0 to 87.5, DASH score ranges from 0 to 11, and MDS ranges from 0 to 9. For all diet quality scores, a higher score is indicative of a higher quality, more healthful diet. Independent of the diet quality scores, reported dietary intake of food group and macronutrients (i.e., grains, fiber, sugar, fruit, vegetables, and proteins) were also compared between lean, NWO, and overweight-obesity groups.

Physical Fitness

Physical fitness was objectively measured by assessing maximal oxygen uptake (VO_2 max) following a modified Balke protocol performed with a trained technician.[42] All VO_2 max tests were conducted on a GE T2100 Treadmill (GE Healthcare). VO_2 max is a measure of cardiorespiratory fitness and captures the ability of the entire cardiovascular system to uptake and utilize oxygen during exercise.[31]

Clinical, Oxidative Stress, and Inflammatory Markers

All blood samples were taken following an overnight fast, processed, and stored for analysis. Fasting lipid profile, metabolic panel, and inflammatory markers were analyzed commercially by Quest Diagnostics. Fasting insulin levels below the level of detection (<2 μIU/mL) were replaced with a value of 1.9 for analyses. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting glucose (mg/dL) divided by 405.[43] An automated machine was used to measure systolic and diastolic blood pressure (Omron). Plasma aminothiol concentrations, including glutathione (GSH), glutathione disulfide, cysteine, and cystine (CySS), were measured using high performance liquid chromatography following published protocols[44] at Emory University. The reduction-oxidation (redox) potentials for the thiol/disulfide couples were calculated using the Nernst equation.[44] The redox potentials provide a measure of the propensity of the redox couples to accept or donate electrons, and a higher value denotes increased oxidative stress. The inflammatory cytokines interleukin-6 (IL-6), IL-8, tumor necrosis factor alpha, and interferon gamma were measured in fasting serum using Fluorokine MultiAnalyte Profiling multiplex kits (R&D Systems) with a Bioplex analyzer (Bio-Rad).

Statistical Analyses

Data are summarized as mean ± standard error for continuous variables or as counts and proportions for categorical variables. Continuous variables that did not appear to have a bell-shaped distribution were natural log transformed for analyses and back transformed to obtain geometric means. To account for zero values in cytokine analyses, a constant of one was added to all values before log transformation. Because the standard error could not be back transformed, 95% CIs along with the geometric mean are presented for log-transformed variables. For categorical variables, χ^2 tests were used to test for differences between the body composition subtypes. Analysis of variance tests were used to examine differences between groups for demographic characteristics that were continuous variables. Overall group differences in the diet quality scores, dietary food groups and macronutrients, and VO_2 max between the body composition subtypes were tested using multiple linear regression analyses, controlling for age (continuous), race (White = 0, other = 1), sex (male = 0, female = 1), and education (college degree, no = 0, yes = 1). Post hoc comparisons between the body composition subtypes were conducted using Tukey's honestly significant different tests. Regression analyses also provided estimates of the group differences in dietary food groups, macronutrients, and clinical and biochemical variables controlling for age (continuous), race (White = 0, other = 1), and sex (male = 0, female = 1) with post hoc comparisons conducted using Tukey adjustment for multiple testing. Multiple linear regression models also were constructed to test for associations between components of body composition and VO_2 max and the diet quality scores, controlling for age (continuous), race (White = 0, other = 1), sex (men = 0, women = 1), and education (college degree, no = 0, yes = 1). Presence of a chronic disease and reported annual household income were also considered as potential confounders but were not included in final models because they were not significantly associated with the body composition subtypes, diet quality scores, or physical fitness level. Finally, interactions of body composition subtypes with race, sex, age and education were tested within the fitted linear models for

Table 1. Demographic and clinical characteristics of 693 adults participating in the Emory-Georgia Tech Predictive Health Initiative cohort from 2007-2013 according to body composition subtype

Characteristic	Lean (n = 100)	Normal Weight Obesity (n = 164)	Overweight-Obesity (n = 429)
	←mean ± standard deviation→		
Age[a] (y)	43.3 ± 12.8[y]	49.1 ± 11.4[z]	50.0 ± 10.9[z]
	←n (%)→		
Sex			
Female	62 (62)	122 (75)	267 (62)*
Male	38 (38)	42 (26)	162 (38)*
Race			
White	81 (83)	120 (74)	287 (68)
African-American, Asian, American Indian	19 (17)	44 (26)	142 (32)
Presence of chronic disease[b]	14 (14)	34 (21)	94 (22)
College degree or higher	90 (90)	137 (84)	342 (80)*
Annual household income[c]			
≤\$50,000	7 (8)	17 (11)	51 (12)
>\$50,000-\$100,000	23 (26)	37 (24)	126 (31)
>\$100,000-\$200,000	31 (34)	60 (39)	145 (35)
>\$200,000	29 (32)	39 (25)	89 (22)

[a]For continuous variables, one-way analysis of variance was performed and results of Tukey post hoc analyses are denoted by superscript letters (y and z) and indicate significant differences between groups for each row. Values that are not connected by the same letter are significantly different at $P < 0.05$.
[b]Chonic diseases include hypertension, diabetes, and hyperlipidemia.
[c]n = 90,153, and 411 for the lean, normal weigh obesity, and overweight-obesity groups, respectively.
*$P < 0.05$ for results of χ^2test that showed a significant difference between the three groups.

the corresponding product terms (e.g., body composition subtype × race, and body composition subtype × sex). All analyses were conducted in JMP Pro software version 13.0.0,[45] using 2-sided tests with a significance level of 0.05.

RESULTS

Demographic and clinical characteristics for all participants are shown in Table 1. BMI and dual energy x-ray absorptiometry body composition data were available for 693 of the study participants of whom 14% were classified as lean, 24% as having NWO, and 62% as having overweight-obesity. There were 14 participants (10 men) with BMI levels in the overweight category and percent body fat values below the sex-specific cut points; these individuals were categorized as lean. There were nine participants (eight women) with BMI levels below 18.5. Seven of these individuals had percent body fat values below the sex-specific cut points and were categorized as lean. One woman had a body fat percent above the sex-specific cut point and was categorized as NWO. The lean group was younger than the NWO and overweight-obesity groups ($P < 0.05$). There was a significant difference in sex distribution between the body composition subtypes ($P = 0.02$). Among all female participants, 14% were categorized as lean, 27% as NWO, 59% as overweight-obesity. Among all male participants, 16% were categorized as lean, 17% as NWO, and 67% as overweight-obesity. The proportion of individuals with a history of chronic disease was comparable between the three groups. The lean group had the highest proportion of participants report attaining a college degree or higher (90%) followed by participants with NWO (84%) and participants with overweight-obesity (80%; $P = 0.047$). There were no differences in reported annual household income between the three groups ($P > 0.05$).

Body Composition and Fat Distribution

Body composition measurements are shown in Table 2. In line with the applied definition of NWO, BMI was similar between the lean and NWO groups and was significantly lower than the overweight-obesity group ($P < 0.05$). Total body fat percent, fat mass, VAT, and WC increased significantly across the three groups from individuals classified as

Table 2. Body composition and fat distribution measures adjusted for age, race, and sex among adult participants in the Emory University-Georgia Tech Predictive Health Initiative cohort from 2007-2013 classified by body composition subtype (n = 693)

Body composition measure[a]	Lean (n = 100)	Normal Weight Obesity (n = 164)	Overweight-Obesity (n = 429)
	←mean ± standard error→		
Body mass index	22.4 ± 0.5[x]	23.0 ± 0.4[x]	31.3 ± 0.2[y]
Body fat (%)	22.6 ± 0.5[x]	31.1 ± 0.4[y]	38.1 ± 0.2[z]
Lean mass (kg)	48.5 ± 0.8[x]	44.1 ± 0.6[y]	52.3 ± 0.4[z]
Fat mass (kg)	14.4 ± 1.0[x]	20.3 ± 0.8[y]	35.0 ± 0.5[z]
Waist circumference (cm)	79.7 ± 1.9[x]	85.7 ± 1.6[y]	101.0 ± 0.9[z]
	←geometric mean (95% CI)→		
Visceral adipose tissue (kg)[b]	0.17 (0.15-0.2)[x]	0.44 (0.39-0.49)[y]	1.21 (1.13-1.3)[z]

[a]Results of multiple linear regression and Tukey post hoc analyses are denoted by superscript letters (x, y, and z) and indicate significant differences between groups for each variable. Within rows, values that are not connected by the same letter are significantly different at $P < 0.05$.

[b]Variable was natural log transformed for analyses and back transformed for data presentation. Because the standard error cannot be back transformed, 95% CIs are shown.

lean to having NWO to having overweight-obesity ($P < 0.05$). Individuals with NWO had the lowest lean mass, which differed significantly between the three groups ($P < 0.05$).

Diet Quality Scores, Dietary Food Groups, and Macronutrients

On average, all diet quality scores reflected similar trends: the lean group reported the highest diet quality but was not significantly different from the NWO group (Figure 1). For AHEI and DASH scores, lean and NWO groups had similar diet quality scores ($P > 0.05$), each with significantly higher scores compared with the overweight-obesity group ($P < 0.05$). For the MDS, only the lean and overweight-obesity groups significantly differed ($P < 0.05$). The association between body composition groups and AHEI differed according to education level ($P = 0.03$), as did the association between body composition groups and MDS ($P = 0.04$). For individuals without college degrees, there were no differences in AHEI or MDS scores across the body composition subtypes, and for individuals with college degrees the pattern was the same as the overall findings. The association between the DASH diet

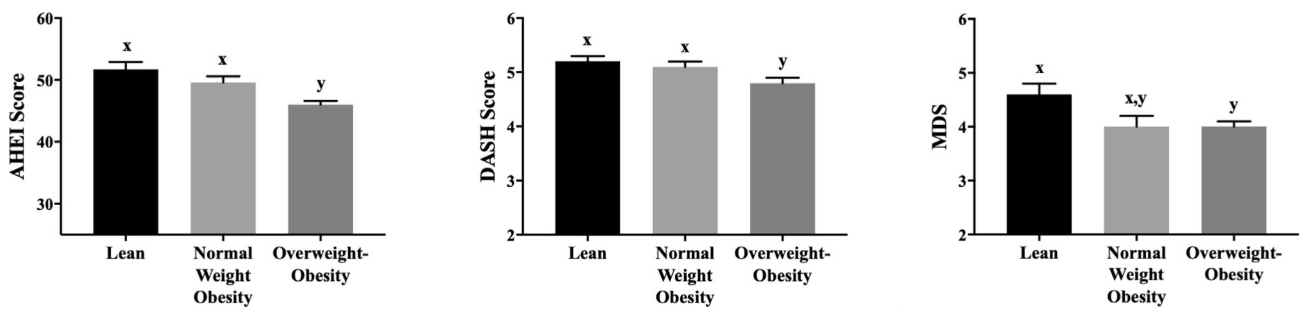

Figure 1. Average (mean ± standard error [SE], adjusting for age, race, sex, and education) reported diet quality scores for participants classified as lean (n = 98), having normal weight obesity (NWO) (n = 162), or as having overweight-obesity (n = 427) participating in the Emory-Georgia Tech Predictive Health Initiative cohort classified according to body composition subtype. Alternate Healthy Eating Index (AHEI) scores were 51.7 ± 1.2 for the lean, 49.6 ± 1.0 for the NWO, and 46.0 ± 0.6 for the overweight-obesity groups. Dietary Approaches to Stop Hypertension (DASH) scores were 5.2 ± 0.1 for the lean, 5.1 ± 0.1 for the NWO, and 4.8 ± 0.1 for the overweight-obesity groups. Mediterranean diet score (MDS) were 4.6 ± 0.2 for the lean, 4.3 ± 0.2 for the NWO, and 4.0 ± 0.1 for the overweight-obesity groups. [a]There was significant effect modification by education status for AHEI and MDS variables. Among individuals without a college degree, there was no difference in AHEI or MDS between the lean, NWO, or overweight-obesity groups ($P > 0.05$). [b]There was significant effect modification by race for DASH score. Among individuals who reported White race, the lean group reported significantly higher DASH diet quality scores compared with the overweight-obesity group ($P < 0.05$). Values in the NWO group were similar to both the lean and overweight/obesity group ($P > 0.05$). Results of Tukey's post hoc analyses are denoted by superscript letters (x and y) and indicate significant differences between groups. Values that are not connected by the same letter are significantly different at $P < 0.05$.

Table 4. Cross-sectional associations between body composition measures, diet quality scores, and physical fitness in 693 adults participating in the Emory Georgia-Tech Predictive Health Initiative cohort from 2007-2013

Body composition measure	AHEI[a]	DASH[b]	MDS[c]	VO_2 max[d] (mL/min/kg)
	←——— β^{e} ± *standard error (*P *value)*[g] ———→			
Body mass index	**−0.09 ± 0.02 (< 0.001)**	**−1.0 ± 0.23 (< 0.001)**	**−0.27 ± 0.13 (0.04)**	**−0.22 ± 0.06 (< 0.001)**
Body fat %	**−0.16 ± 0.02 (< 0.001)**	**−1.54 ± 0.26 (< 0.001)**	**−0.73 ± 0.15 (< 0.001)**	**−0.35 ± 0.03 (< 0.001)**
Lean mass (kg)	−0.02 ± 0.03 (0.45)	−0.42 ± 0.29 (0.15)	0.17 ± 0.16 (0.29)	**−0.11 ± 0.04 (0.003)**
Fat mass (kg)	**−0.21 ± 0.04 (< 0.001)**	**−2.05 ± 0.47 (< 0.001)**	**−0.71 ± 0.26 (0.008)**	**−0.52 ± 0.05 (< 0.001)**
Visceral adipose tissue[f] (kg)	**−0.02 ± 0.003 (< 0.001)**	**−0.18 ± 0.04 (< 0.001)**	**−0.06 ± 0.02 (0.003)**	**−0.04 ± 0.004 (< 0.001)**
Waist circumference (cm)	−0.15 ± 0.08 (0.05)	−1.00 ± 0.80 (0.21)	−0.37 ± 0.47 (0.43)	**−0.63 ± 0.11 (< 0.001)**

[a]All coefficient estimates are from multiple linear regression analyses with body composition measures as a continuous variable. Analyses were conducted individually for each measure of body composition. All estimates are adjusted for age, race, sex, and education.
[b]AHEI = Alternate Healthy Eating Index.
[c]DASH = Dietary Approaches to Stop Hypertension.
[d]MDS = Mediterranean Diet Score.
[e]VO_2 max = maximal oxygen uptake.
[f]Variable was log transformed for analyses.
[g] Statistically significant results are bolded within the table.

quality score and body composition groups differed according to race ($P = 0.008$). Among individuals who reported White race, DASH diet quality scores differed only between the lean and overweight-obesity groups with the NWO group reporting similar scores to both. Among other race categories, only the NWO group reported higher DASH diet quality scores than the overweight-obesity group. These results should be interpreted with caution due to the post hoc nature of these analyses. Stratified analyses with sex as a biological variable are reported in Table 3 (available at www.jandonline.org). In multiple linear regression analyses, all diet quality scores were significantly, inversely associated with measures of body fat and VAT ($P < 0.001$ for all) but were not associated with measures of WC (Table 4). In comparisons of reported daily food group and macronutrient consumption, participants with overweight-obesity reported significantly higher consumption of saturated fats, *trans* fats, and meats and significantly lower consumption of carbohydrates, fiber, fruits and legumes, nuts, and soy compared with lean and NWO participants (Table 5 available at www.jandonline.org) ($P < 0.05$ for all). The NWO group reported lower consumption of total fat and protein, refined grains and significantly higher consumption of yellow/orange vegetables than the overweight-obesity group ($P < 0.05$ for all). Only reported potato consumption differed significantly between each group ($P < 0.05$).

Physical Fitness

Fitness levels were incrementally lower across the three groups ($P < 0.05$), with the NWO and overweight-obesity groups having significantly lower fitness levels compared with the lean group (Figure 2). There was significant effect modification between VO_2 max and age ($P = 0.046$). Among individuals with NWO, there was a significant decline in VO_2 max with aging. Analyses of VO_2 max stratified by sex are shown in Table 3 (available at www.janonline.org). In multiple linear regression analyses, VO_2 max was inversely associated with all measures of total and abdominal adiposity (Table 4) ($P < 0.001$ for all).

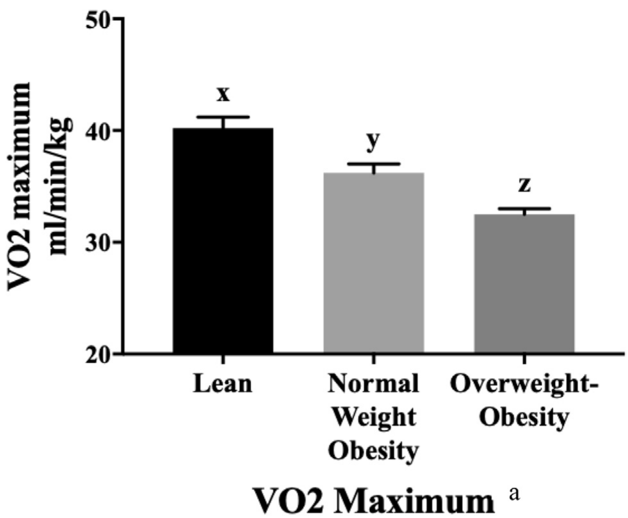

Figure 2. Average (mean ± standard error [SE], adjusting for age, race, sex, and education) maximal oxygen uptake (VO2) maximum values for participants classified as lean (n = 91), having normal weight obesity (NWO) (n = 154), or as having overweight-obesity (n = 383) participating in the Emory-Georgia Tech Predictive Health Initiative cohort classified according to body composition subtype. VO2 maximum values were 40.2 ± 1.0 mL/min/kg for the lean, 36.2 ± 0.8 mL/min/kg for the NWO, and 32.5 ± 0.5 mL/min/kg for the overweight-obesity groups. [a]There was significant effect modification between age and VO2 maximum. Among individuals with NWO, there was a significant decline in VO2 maximum with aging. Results of Tukey's post hoc analyses are denoted by superscript letters (x, y, and z) and indicate significant differences between groups. Values that are not connected by the same letter are significantly different at $P < 0.05$.

Table 6. Clinical, oxidative stress, and inflammatory markers adjusted for age, race, and sex in 693 adults participating in the Emory-Georgia Tech Predictive Health Initiative cohort from 2007-2013 classified according to body composition subtype

Biomarker[a]	Lean (n = 100)	Normal Weight Obesity (n = 164)	Overweight-Obesity (n = 429)
	←geometric mean (95% CI)→		
Blood glucose[b] (mg/dL)[cd]	86.0 (83.6-88.5)[x]	86.0 (84.1-88.0)[x]	90.2 (89.0-91.5)[y]
Insulin[b] (μIU/mL)[ef]	2.41 (2.07-2.8)[x]	3.09 (2.74-3.48)[y]	5.41 (5.03-5.82)[z]
HOMA-IR[beg]	0.51 (0.44-0.60)[x]	0.66 (0.58-0.75)[y]	1.21 (1.11-1.3)[z]
	←mean ± standard error→		
Total cholesterol (mg/dL)[h]	185.0 ± 3.8[x]	196.9 ± 3.0[y]	191.7 ± 1.9[xy]
Low-density lipoprotein cholesterol (mg/dL)[h]	98.4 ± 3.4[x]	113.0 ± 2.7[y]	113.0 ± 1.6[y]
High-density lipoprotein cholesterol (mg/dL)[h]	72.1 ± 1.7[x]	65.2 ± 1.3[y]	56.5 ± 0.8[z]
Triglyceride (mg/dL)[ij]	72.2 ± 6.0[x]	93.8 ± 4.8[y]	112.4 ± 3.0[z]
Systolic blood pressure (mm Hg)[k]	114.9 ± 1.5[x]	116.9 ± 1.2[x]	125.9 ± 0.7[y]
Diastolic blood pressure (mm Hg)[k]	72.3 ± 1.1[x]	75.6 ± 0.9[x]	79.2 ± 0.5[y]
Cysteine (μM)[l]	8.9 ± 0.2[x]	9.2 ± 0.2[x]	9.4 ± 0.1[x]
Cystine (μM)[l]	78.7 ± 1.8[x]	79.7 ± 1.4[x]	87.9 ± 0.9[y]
	←geometric mean (95% CI)→		
Glutathione[b] (μM)[l]	1.77 (1.64-1.91)[x]	1.76 (1.66-1.87)[x]	1.5 (1.45-1.56)[y]
Glutathione disulfide[b] (μM)[l]	0.052 (0.045-0.06)[x]	0.053 (0.048-0.06)[x]	0.049 (0.045-0.052)[x]
	←mean ± standard error→		
E_h Cysteine (mV)[lm]	−69.7 ± 0.6[x]	−70.3 ± 0.5[x]	−69.5 ± 0.3[x]
E_h Glutathione (mV)[lm]	−137.3 ± 1.1[x]	−136.9 ± 0.8[x]	−134.0 ± 0.5[y]
	←geometric mean (95% CI)→		
Cystine/glutathione ratio[bl]	43.5 (39.8-47.7)[x]	44.6 (41.5-47.8)[x]	57.3 (54.8-59.8)[y]
Interleukin-6[b] (pg/mL)[no]	2.51 (1.99-3.18)[x]	2.54 (2.11-3.06)[x]	3.1 (2.76-3.48)[x]
Tumor necrosis factor-α[b] (pg/mL)[np]	3.25 (2.88-3.66)[x]	3.47 (3.16-3.81)[x]	3.64 (3.43-3.85)[x]
Interleukin-8[b] (pg/mL[nq]	7.87 (6.9-8.98)[x]	7.96 (7.18-8.82)[x]	7.91 (7.42-8.43)[x]
Interferon-γ[b] (pg/mL)[nr]	0.35 (0.25-0.5)[x]	0.32 (0.25-0.42)[x]	0.42 (0.35-0.49)[x]

[a]Results of multiple linear regression and Tukey post hoc analyses are denoted by superscript letters (x, y, and z) and indicate significant differences between groups for each value. Within each row, values that are not connected by the same letter are significantly different at $P < 0.05$.
[b]Variable was natural log transformed for analyses and back transformed for data presentation.
[c]To convert mg/dL glucose to mmol/L, multiple mg/dL by 0.0555.
[d]n=162 and 427 for the normal weight obesity and overweight-obesity groups, respectively.
[e]n=162 and 426 for the normal weight obesity overweight-obesity groups, respectively
[f]To convert μIU/mL insulin to pmol/L, multiply μIU/mL by 6.0.
[g]HOMA-IR = homeostasis model assessment of insulin resistance.
[h]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259.
[i]n=161 and 426 for the normal weight obesity and overweight-obesity groups, respectively.
[j]To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113.
[k]n=163 and 429 in the normal weight obesity and overweight-obesity groups, respectively.
[l]Aminothiol redox measures: n = 93, 155, and 412 for the lean, normal weight obesity, and overweight-obesity groups, respectively.
[m]E_h millivolts = redox potential.
[n]Cytokine measure.
[o]n = 93, 155, and 415 for the lean, normal weight obesity, and overweight-obesity groups, respectively.
[p]n = 95, 159, and 418 for the lean, normal weight obesity, and overweight-obesity groups, respectively.
[q]n = 94, 157, and 415 for the lean, normal weight obesity, and overweight-obesity groups, respectively.
[r]n = 93, 156, and 416 for the lean, normal weight obesity, and overweight-obesity groups, respectively.

Clinical, Oxidative Stress, and Inflammatory Markers

Fasting glucose concentrations were similar in the lean and NWO groups and significantly higher in the overweight-obesity group (Table 6) ($P < 0.05$). Fasting insulin concentrations and HOMA-IR were significantly different between each group, with the NWO group exhibiting values

between the other two groups ($P < 0.05$). Total cholesterol was higher in the NWO group compared with the lean group ($P < 0.05$). Low-density lipoprotein cholesterol levels were similar in the NWO and overweight-obesity groups and significantly elevated compared with the lean group ($P < 0.05$). High-density lipoprotein cholesterol and triglyceride levels differed significantly between each group ($P < 0.05$ for both). Systolic and diastolic blood pressure were significantly higher in the overweight-obesity group compared with the lean and NWO groups ($P < 0.05$). All plasma aminothiol concentrations were similar between lean participants and individuals with NWO ($P > 0.05$) and reflected a less oxidized redox state compared with the overweight-obesity group who exhibited higher CySS, lower GSH, higher GSH redox potential, and higher CySS/GSH ratio. Inflammatory cytokines did not differ between the three groups ($P > 0.05$ for all).

DISCUSSION

NWO is associated with cardiometabolic derangements that place seemingly lean individuals at risk for metabolic disease.[8-15] Notably, more adults in this cohort were classified as NWO than were classified as lean. Individuals with NWO had significantly lower physical fitness levels compared with their lean counterparts. Individuals with NWO reported higher diet quality than individuals classified as having overweight-obesity, although higher diet quality was inversely associated with measures of adiposity in all participants regardless of weight status. Furthermore, the metabolic panel of individuals with NWO indicated higher levels of risk factors for cardiometabolic disease, particularly in markers of insulin resistance and lipid concentrations.

Individuals with NWO have a higher chronic disease and mortality risk compared with normal-weight, lean individuals or metabolically healthy, obese individuals,[8,15-17] and the definition used to classify individuals with NWO plays an important role in establishing these risks. Oliveros and colleagues[9] describe the history of investigating subtypes of obesity and summarize the metabolic dysfunction noted in individuals with NWO. The prevalence of NWO has been reported as high as 30% and differs by race and sex.[8,10] There are no established percent body fat cut points to define obesity,[46] which contributes to the variability in reported prevalence.[46,47] One study found the prevalence of NWO in women ranged from 1.4% to 27.8% when applying various thresholds.[47] Using age- and sex-specific cut points may decrease the variability in prevalence.[47] In this cohort, there was a 24% prevalence of NWO among all participants, a 27% prevalence of NWO among women, and a 17% prevalence of NWO among men. Additional reports are generally consistent that women have a higher prevalence of NWO than men.[47-50] However, a recent nationwide study of Chinese adults noted a higher prevalence of NWO in males (9.5% vs 6.1%),[14] showing the importance of screening for NWO in both men and women. In addition, obesity misclassification by BMI may differ by sex.[51] One study showed men were more likely to be misclassified at a BMI between 25 and 27, but women were more likely to be misclassified at a BMI between 24 and 26.[51] Altogether, although the prevalence and definition of NWO is variable, there is strong evidence from the current study and other studies that supports increased cardiometabolic and mortality risk factors in individuals with normal weight but high body fat and a need to effectively screen and identify these individuals.[8-15,17,52]

The NWO group in this study had significantly lower levels of objectively measured physical fitness compared with the lean group. Similarly, a study using objective assessments reported impaired physical fitness and muscular strength in college-aged individuals in China with NWO.[53] Measures of self-reported physical activity participation data have shown mixed results.[54,55] Circuit training has been successfully applied as a 10-week physical activity intervention in women with NWO,[56] showing significant improvements in clinical measures and reductions in total and trunk body fat that resulted in participants no longer being classified as NWO.[56] Low physical fitness is a leading risk factor for chronic diseases,[57] and increasing participation in aerobic physical activity is an effective primary and secondary prevention strategy to reduce chronic disease risk.[58] The health benefits from aerobic physical activity participation may exceed the effects of prescription medications.[59] Thus, there is a need to address the low levels of physical fitness in this population to reduce disease risk.

Much attention in NWO research is paid to increased adiposity; however, another important characteristic of NWO indicated by this study is decreased lean mass. Physical activity, especially strength training, is integral for stimulating skeletal muscle protein synthesis and maintaining lean mass, particularly as one ages.[60] Further, physical activity improves glucose metabolism and insulin sensitivity, and individuals with higher fitness levels have better insulin sensitivity.[61] Skeletal muscle secretes a variety of myokines, especially during exercise, such as follistatin-like 1, fibroblast growth factor-21, brain-derived neurotrophic factor, myonectin, and IL-6, that have both local and systemic health-promoting effects.[59] These chemicals increase glucose uptake, promote uptake and lipolysis of free fatty acids in skeletal muscle and the liver, have neurocognitive benefits, promote angiogenesis, improve endothelial function, and protect against ectopic fat deposition.[59] Thus, strategies designed to increase lean mass in individuals with NWO may be an important factor to target for health improvements through a variety of mechanisms.

Higher diet quality is associated with decreased chronic disease risk.[19-23,25-28] In this study, individuals with NWO reported similar diet quality as lean individuals and higher diet quality than individuals classified as having overweight-obesity, with group differences primarily driven by women. There were few similarities in reported food group and macronutrient intakes between NWO and overweight-obesity groups. Diet quality scores reflected suboptimal diet quality for all groups, although the average AHEI score for all groups was above a previously reported US average.[62] Few studies have investigated dietary intake or diet quality of individuals with NWO.[54,55,63] Mannisto and colleagues[54] found components of dietary intake related to diet quality were associated with NWO, including lower intakes of cereals, fish, and root vegetables, and higher intakes of sugar. Amani and colleagues[63] found that individuals with NWO

consumed lower amounts of antioxidant compounds compared with lean individuals and had similar total antioxidant capacity as individuals categorized as having overweight-obesity. Further, the NWO group consumed higher total energy, less fiber, and fewer servings of fruit, legumes, and nuts and seeds compared with the lean group.[63] Notably, in the entire cohort, higher diet quality was associated with lower total body fat and VAT. In longitudinal studies, poor diet quality has been shown to predict higher visceral adiposity, and interventions that increase physical activity and/or improve diet quality have been effective in reducing VAT and liver fat while improving cardiometabolic risk factors.[64-66] Although diet quality may not differentiate individuals with NWO from lean individuals in this cohort, maintaining a higher diet quality may help prevent additional weight gain.

In the current study, individuals with NWO and overweight-obesity exhibited adverse metabolic biomarkers compared to the lean group, including fasting insulin concentrations, HOMA-IR, total cholesterol, and low-density lipoprotein cholesterol levels. There is substantial evidence of cardiometabolic dysregulation in NWO cohorts, including dyslipidemia,[9,10,12,50,67,68] increased inflammation,[12,13] increased oxidative stress,[11,13] altered adipokine levels,[8,11] and the presence of metabolic syndrome components, including hypertension, insulin resistance, and hyperglycemia.[10,11,14,16,17,48,69-71] In this cohort, although individuals with NWO showed dysregulated insulin function and altered lipid levels compared with lean individuals, there was no evidence of significant oxidative stress or inflammation in the NWO group compared with the lean group. We previously reported that higher diet quality is associated with lower levels of oxidative stress.[24] It is possible that individuals with NWO in the current cohort maintain a diet quality high enough to sustain aminothiol redox balance. Although there is heterogeneity in reported metabolic profiles of individuals with NWO, there is consistent evidence of adverse metabolic health in these individuals, highlighting the need to screen for and prevent NWO.[9,10,12,15,50,67,68]

Major strengths of this study were the use of sensitive body composition and fat distribution assessment methods in a large cohort of adults to classify body composition subtypes. This study also provides extensive clinical and metabolic phenotyping of individuals with NWO to add to the existing literature of the adverse clinical profiles presented in individuals with NWO. There are also some limitations to this study. Food frequency questionnaires are subject to recall bias, have a high participant burden, and varying reliability.[72,73] This was a cross-sectional analysis, and causality cannot be inferred in the reported relationships. Participants in this cohort reported high education and income levels, which may limit the generalizability of this population. Future research should examine the most appropriate cut points for defining obesity considering age, sex, and race. Of note, additional classifications exist for individuals with a normal weight but increased disease risk such as metabolically obese, normal weight,[3] lean insulin resistant,[74] lean with type 2 diabetes,[75] and nonalcoholic steatohepatitis in lean individuals.[76] Many of these classifications are based on BMI, whereas NWO is classified by body fat percent and BMI. Indeed, many of these noted classifications are a subset of individuals with NWO with underlying obesity, abdominal adiposity, and inflammation as a driver of cardiometabolic disease.[77,78] Finally, in addition to diet and physical fitness, numerous factors influence body weight and composition and metabolic health, including genetics, epigenetics, and environmental exposures, which are not addressed here.[79,80]

CONCLUSIONS

Although diet quality was similar between individuals with NWO and lean individuals, physical fitness was significantly lower in the NWO group. Focus on increasing physical activity and physical fitness may be an important lifestyle factor to target for risk reduction in individuals with NWO. Future research should determine whether achieving an adequately high diet quality with concomitant increase in physical activity is an effective strategy for individuals with NWO to reduce fat mass and increase muscle synthesis.

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For more information on the subject discussed in this article, see Sites in Review on page 2110.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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AUTHOR CONTRIBUTIONS

M. P. Bellissimo, J. A. Alvarez, and T. R. Ziegler formulated the research question. T. R. Ziegler and D. P. Jones had leading roles in the cohort study design, implementation, and data collection. M. P. Bellissimo, J. N. Binongo, and J. A. Alvarez conducted data analyses, and E. L. Bettermann, P. H. Tran, B. H. Crain, T. J. Hartman, and E. P. Ferranti assisted in data acquisition and analyses. M. P. Bellissimo drafted the manuscript with J. A. Alvarez and T. R. Ziegler. All authors read and approved the final manuscript.

Table 3. Comparisons of diet quality scores and physical fitness adjusting for age and race among 687 adults within the Emory University-Georgia Tech Predictive Health Initiative cohort from 2007-2013 classified into three body composition subtypes and stratified by sex

Diet quality score or fitness measure[a]	Lean	Normal Weight Obesity	Overweight-Obesity
	←—— *mean ± standard error*		——→
Female participants			
Alternate Healthy Eating Index[b]	55.0 ± 1.5^{x}	51.4 ± 1.1^{x}	47.3 ± 0.7^{y}
DASH Score[bc]	5.2 ± 0.1^{x}	5.0 ± 0.1^{x}	4.7 ± 0.1^{y}
Mediterranean Diet Score[b]	5.0 ± 0.2^{x}	4.4 ± 0.2^{xy}	4.0 ± 0.1^{y}
VO_2 max (mL/min/kg)[d]	37.4 ± 1.2^{x}	32.6 ± 0.8^{y}	28.9 ± 0.5^{z}
Male participants			
Alternate Healthy Eating Index[b]	50.1 ± 1.9^{x}	48.1 ± 1.7^{x}	47.0 ± 1.1^{x}
DASH Score[b]	5.3 ± 0.2^{x}	5.3 ± 0.2^{x}	5.0 ± 0.1^{x}
Mediterranean Diet Score[b]	4.6 ± 0.3^{x}	4.6 ± 0.3^{x}	4.4 ± 0.2^{x}
VO_2 max[d] (mL/min/kg)	44.4 ± 1.7^{x}	41.4 ± 1.5^{y}	38.1 ± 1.0^{y}

[a]Results of multiple linear regression and Tukey post hoc analyses are denoted by superscript letters (x, y, and z) and indicate significant differences between groups for each row. Within rows, values that are not connected by the same letter are significantly different at $P < 0.05$.

[b]n = 62,121, and 267 in the lean, normal weight obesity, and overweight-obesity groups, respectively, in women and n = 36, 41, and 160 in the lean, normal weight obesity, and overweight-obesity groups, respectively, in men.

[c]DASH = Dietary Approaches to Stop Hypertension.

[d]VO2 max = maximal oxygen uptake. n=57, 116, and 232 in the lean, normal weight obesity, and overweight-obesity groups, respectively in women and n = 34, 38, and 151 in the lean, normal weight obesity, and overweight-obesity groups, respectively in men.

Table 5. Comparison of reported daily intake of food groups and macronutrients per 1,000 kcal adjusted for age, race, and sex between 687 adults within the Emory-Georgia Tech Predictive Health Initiative cohort from 2007-2013 categorized into body composition subtypes

Food group/macronutrient variable[a]	Lean (n = 98)	Normal Weight Obesity (n = 162)	Overweight-Obesity (n = 427)
	←	*mean ± standard error*	→
Total fat[b] (g)	38.6 ± 0.7[yz]	38.4 ± 0.6[y]	40.4 ± 0.4[z]
	←	*geometric mean (95% CI)*	→
Saturated fat[c]	10.4 (9.8-10.9)[y]	10.3 (9.9-10.7)[y]	11.2 (11.0-11.5)[z]
	←	*mean ± standard error*	→
Monounsaturated fat[b]	15.4 ± 0.3[x]	15.4 ± 0.3[x]	16.1 ± 0.2[x]
	←	*geometric mean (95% CI)*	→
Polyunsaturated fat[c]	9.3 (8.9-9.8)[x]	9.3 (8.9-9.6)[x]	9.5 (9.3-9.7)[x]
Trans fat[c]	0.9 (0.8-1)[y]	0.9 (0.8-0.9)[y]	1.1 (1.1-1.2)[z]
	←	*mean ± standard error*	→
Total carbohydrates[b] (g)	123.6 ± 2.0[y]	125.6 ± 1.6[y]	118.3 ± 1.0[z]
Total grains[b] (oz equivalents)	2.9 ± 0.1[x]	2.6 ± 0.1[x]	2.8 ± 0.04[x]
Whole grains[b]	0.9 ± 0.1[y]	0.8 ± 0.04[yz]	0.7 ± 0.03[z]
Refined grains[b]	2.0 ± 0.1[yz]	1.9 ± 0.1[y]	2.1 ± 0.04[z]
	←	*geometric mean (95% CI)*	→
Total dietary fiber[c] (g)	12.1 (11.3-12.9)[y]	11.7 (11.1-12.4)[y]	10.7 (10.4-11.1)[z]
Added sugars[c] (tsp equivalents)	5.6 (5.1-6.1)[x]	5.5 (5.1-6.0)[x]	5.4 (5.2-5.7)[x]
Total fruits[c] (c)	0.8 (0.7-0.9)[y]	0.8 (0.8-0.9)[y]	0.6 (0.6-0.7)[z]
Whole fruit[c]	0.6 (0.5-0.6)[y]	0.6 (0.5-0.7)[y]	0.4 (0.4-0.5)[z]
Total vegetables[c] (c)	1.2 (1.1-1.3)[x]	1.3 (1.2-1.4)[x]	1.2 (1.1-1.2)[x]
Yellow/orange[c]	0.08 (0.07-0.1)[yz]	0.1 (0.08-0.11)[y]	0.07 (0.07-0.08)[z]
Dark leafy greens[c]	0.03 (0.02-0.03)[x]	0.03 (0.02-0.03)[x]	0.03 (0.02-0.03)[x]
Potatoes[c]	0.08 (0.07-0.09)[x]	0.10 (0.09-0.11)[y]	0.12 (0.11-0.12)[z]
Total protein[c] (g)	38.2 (36.8-39.7)[yz]	37.2 (36.1-38.3)[y]	39.5 (38.8-40.2)[z]
Milk and dairy products[c] (milk equivalents[d])	0.5 (0.5-0.6)[x]	0.5 (0.5-0.6)[x]	0.6 (0.5-0.6)[x]
Eggs[c] (n)	0.1 (9.6-0.2)[x]	0.1 (0.1-0.1)[x]	0.1 (0.1-0.2)[x]
Beef, pork, and lamb[c] (oz)	0.3 (0.3-0.4)[y]	0.4 (0.3-0.5)[y]	0.5 (0.5-0.6)[z]
Poultry[c] (oz)	0.3 (0.2-0.3)[y]	0.3 (0.2-0.3)[y]	0.4 (0.3-0.4)[z]
Fish/seafood[c] (oz)	0.3 (0.3-0.4)[x]	0.3 (0.2-0.4)[x]	0.4 (0.3-0.4)[x]
Beans/legumes/nuts/soy[c] (servings)	1.7 (1.4-2.0)[y]	1.6 (1.4-1.8)[y]	1.2 (1.1-1.3)[z]

[a]Results of Tukey post hoc analyses are denoted by superscript letters (x, y, and z) and indicate significant differences between groups for each row. Within each row, values that are not connected by the same letter are significantly different at $P < 0.05$.
[b]Normally distributed data.
[c]Variable was natural log-transformed for analyses and back transformed for data presentation.
[d]A milk equivalent is equal to consumption of 1 c low-fat milk.