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Race-Ethnic Differences in Adipokine Levels: The Study of Women's Health Across the Nation (SWAN)

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Abstract

Objective—Differences in adipose tissue secretory profile, as measured by adipokine levels, may play a role in race-ethnic disparities in cardiovascular disease (CVD). We examined race-ethnic differences in adipokine levels in a group of mid-life Caucasian, African American (AA), Chinese and Japanese women, after accounting for adiposity.

Methods—Data on 1876 women from the Study of Women's Health Across the Nation were analyzed. In multivariable adjustment, including total fat mass, differences in total and high molecular weight (HMW) adiponectin, leptin and soluble leptin receptor (sOB-R) levels were examined.

Results—Despite intermediate levels of adiposity, Caucasian women had higher levels of both total and HMW adiponectin, when compared to both AA and Chinese and Japanese women. After multivariable adjustment, compared to Caucasian women, AA women had significantly lower total (β : -3.40; 95%CI: -4.29, -2.52; $p < 0.001$) and HMW adiponectin (β : -0.53; 95%CI: -0.64, -0.43; $p < 0.001$) levels, higher leptin levels (β : 3.26; 95%CI: 1.36, 5.16; $p < 0.001$) and lower sOB-R levels (β : -0.07; 95%CI: -0.11, -0.03; $p < 0.001$). Compared to Caucasian women, both Chinese

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Unab I. Khan was involved in the design and conduct of the study, data analysis, interpretation and manuscript writing. Maryfran R. Sowers (deceased), Peter Mancuso, and Rachel P. Wildman were involved in the design and conduct of the study, data collection and analysis, data interpretation and manuscript writing. Susan Everson-Rose and Philip Scherer were involved in data interpretation and manuscript writing. Dan Wang was involved in data analysis, data interpretation and manuscript writing.

and Japanese women had lower total (Chinese: β : -5.50; 95%CI: -7.07, -3.93; $p < 0.001$; Japanese: β : -5.48; 95%CI: -6.95, -4.02; $p < 0.001$) and HMW adiponectin (Chinese: β : -0.57; 95%CI: -0.75, -0.38; $p < 0.001$; Japanese: β : -0.61; 95%CI: -0.78, -0.44; $p < 0.001$) levels and lower sOB-R levels (Chinese: β : -0.13; 95%CI: -0.20, -0.06; $p < 0.001$; Japanese: β : -0.09; 95%CI: -0.15, -0.02; $p = 0.008$).

Conclusions—Significant race-ethnic differences exist in circulating adipokines, even after accounting for adiposity. Further research is needed to explicitly determine if such differences contribute to known racial differences in CVD risk.

Keywords

Adiponectin; High Molecular Weight Adiponectin; Leptin; Soluble Leptin Receptor

INTRODUCTION

The discrepancy in cardiovascular disease (CVD) morbidity and mortality across race-ethnic groups has been postulated to result from the differential impact of obesity and its related comorbidities such as hypertension and diabetes in race-ethnic and socioeconomic groups. [1] In recent years, there has been a recognition of the role of adipose tissue distribution, rather than total body size, in increasing CVD risk. However, neither body mass index (BMI), the clinical measure of obesity, nor differences in adipose tissue distribution are able to completely explain differences in CVD risk among race-ethnic groups. For example, even after adjusting for BMI, compared to Caucasians, African Americans (AA) have a more favorable adipose tissue distribution profile, with a greater percentage of peripheral than central adipose tissue,[2] which should lead to a more favorable CVD risk profile. However, epidemiologic data consistently show higher prevalence of CVD, hypertension and cancer in AA vs. Caucasian groups.[3] Similarly, the limited data in Asian Americans shows worse cholesterol profiles[4] and a higher prevalence of diabetes[5] despite lower levels of adiposity. With our growing understanding of adipose tissue as a dynamic and functional organ, the secretory profile of adipose tissue, as measured by adipokine levels, is now being investigated for its role in race-ethnic disparities in CVD risk profiles. At present, limited data are available examining race-ethnic differences in adipokine levels.

Adiponectin, the most abundant adipose tissue-specific adipokine in circulation,[6] plays a protective role in CVD risk. It improves peripheral insulin sensitivity, improves fatty acid oxidation in liver and muscle[7] and induces the production of anti-inflammatory cytokines. [8, 9] Low levels of adiponectin are associated with obesity,[6] type 2 diabetes,[10] metabolic syndrome,[11] and atherosclerosis.[12–14] Of the various isoforms of adiponectin, high molecular weight adiponectin (HMW adiponectin) represents the most potent and biologically active form.[15] Leptin, another adipokine, plays a role in energy homeostasis by affecting satiety.[16, 17] Leptin also augments glucose and lipid metabolism and up-regulates the expression of pro-inflammatory and pro-angiogenic factors.[18, 19] It has been independently associated with obesity, decreased arterial distensibility,[20] subclinical atherosclerosis,[21] and independently predicts CVD events in patients with and without established CVD.[22, 23] Leptin acts by binding to specific leptin receptors.[24] Of the six known isoforms, soluble leptin receptor (sOB-R) binds leptin in the serum,[25] and modulates serum leptin levels by delaying clearance and determining the amount of free versus bound leptin, thus playing an important role in leptin homeostasis.[26] There is an inverse and curvilinear correlation between leptin and sOB-R; increasing adiposity decreases sOB-R levels.[27] Obese subjects have higher levels of leptin circulating in the free form suggesting that the leptin-binding proteins are saturated in states of increased adiposity.[28]

The purpose of the current study was to compare levels of total and HMW adiponectin, leptin and sOB-R among mid-life Caucasian, African American, Chinese/Chinese American and Japanese/Japanese American women, after accounting for differences in fat mass.

METHODS

Study Population

The current study included participants from the Study of Women's Health Across the Nation (SWAN), a community-based, multicenter, multiethnic longitudinal study designed to characterize the biological and psychosocial changes that occur during the menopausal transition. Briefly, SWAN is being conducted at seven sites: Boston; Chicago; the Detroit area; Los Angeles; Newark, NJ; Pittsburgh, PA; and Oakland, CA. From 1996 to 1997, 3,302 women aged 42–52 years were enrolled. Each site recruited Caucasian women plus one race-ethnic group: African American (Pittsburgh, Chicago, Michigan and Boston), Chinese/Chinese American (Oakland), Japanese/Japanese American (UCLA) and Hispanic (Newark). Complete information on screening and data collection has been published previously.[29] The institutional review boards of the participating institutions approved this study, and informed consent was obtained.

The current report utilizes data collected from the 2,310 women present at the sixth annual SWAN follow-up visit, the only visit at which both fat mass and adipose hormones were available on the full SWAN cohort. After excluding 428 women missing key covariates of interest, data from 1,882 women were available for the current analyses (951 Caucasian, 535 African American, 175 Chinese, 215 Japanese and 6 Hispanic women). Due to the small number of Hispanic women in the sample, data on these women were excluded. Therefore, the present analyses report findings from 1,876 participants.

Body Size and Composition Measures

Height and weight were measured in light clothing without shoes and using calibrated scales. Body mass index was calculated as weight in kilograms divided by height in (meter)². Waist circumference was measured in non-restrictive undergarments, or in cases where respondents refused, measures were taken over light clothing. Waist circumference was measured at the level of the natural waist, defined as the narrowest part of the torso as seen from the anterior aspect. In cases where a waist narrowing was difficult to identify, the measure was taken at the smallest horizontal circumference in the area between the ribs and the iliac crest. Bioelectrical impedance analysis (BIA) was used to measure total fat mass. [30],[31]

Blood Assays

Standard cardiovascular risk factors were assayed at the Medical Research Laboratories (Lexington, KY), certified by the National Heart Lung and Blood Institute, Centers for Disease Control and Prevention Part II program, as previously described. [32] The homeostasis model assessment insulin resistance index (HOMA-IR) was calculated from fasting insulin and glucose [fasting insulin ($\mu\text{U/ml}$) $\times$ fasting glucose (mmol/l)]/22.5. [33] High sensitivity C-reactive protein (CRP) levels were measured using an ultra-sensitive rate immunonephelometric method (BN 100, Dade-Behring, Marburg, Germany). Leptin, sOB-R, total and HMW adiponectin were determined in Dr. Peter Mancuso's laboratory, in duplicate, using commercially available colorimetric enzyme immunoassay kits according to the manufacturer's instructions (leptin, adiponectin, and HMW adiponectin, Millipore, St. Charles, MO and sOB-R, R & D systems, Minneapolis, MN). The mean coefficient of variation percent (CV %) for duplicate samples for each subject and lower limit of detection,

respectively, were: adiponectin: 5.4%, 0.78 ng/ml; HMW adiponectin: 8.1%, 0.5 ng/ml; leptin: 4%, 0.5 ng/ml; and sOB-R: 3.7%, 0.31 ng/ml.

Questionnaire Data

Race, current smoking habits and education status (high school / post high school / college) were obtained from a self-reported questionnaire. Women were asked about their menstrual bleeding patterns in the 12 months prior to recruitment and divided into categories similar to the World Health Organization: 1) Premenopause: Monthly bleeding with no perceived change in cycle interval; 2) Early Perimenopause: Monthly bleeding with a perceived change in cycle interval, but at least one period within the past three months; 3) Late Perimenopause: >3 consecutive months of amenorrhea, with at least one period in the last 12 months; 4) Post Menopause: >12 consecutive months of amenorrhea; 5) Surgical Menopause: Menopause induced by hysterectomy with/without oophorectomy; 6) MHT users: Use of menopausal hormone therapy before the documentation of a final menstrual period. For the present analysis, we combined the Pre/Early Perimenopause groups and compared them to the Late/ Post Menopause/Surgical Menopause groups and the MHT users. Physical activity was based on the Kaiser Permanente Activity Score.[34]

Statistical Analysis

Demographics, metabolic risk factors, body fat measurements and adipokine levels were compared among the four race-ethnic groups (Caucasian, African American, Chinese and Japanese) using the chi-square test for categorical variables and one-way analysis of variance (ANOVA) for normally distributed continuous variables. Pair-wise comparisons were tested when significant differences were found. The Wilcoxon rank-sum test was used for skewed continuous data.

The strength of association between each adipokine and adiposity measure in the race-ethnic groups was measured using Spearman's correlation.

In a series of regression models, using continuous levels of each adipokine (log-transformed values for HMW adiponectin and sOB-R) as the dependent variable, differences in adipokine levels between the race-ethnic groups were examined. Models were initially adjusted for age, site of recruitment, education level, smoking, physical activity, menopause status and total fat mass, followed by adjustment for waist circumference (as a surrogate measure of central obesity) in lieu of total fat mass, and further adjustment for HOMA and CRP. There was minimal overlap in total fat mass between African American and both Chinese and Japanese women. Therefore, two sets of regression analyses were carried out: the first comparing differences between Caucasian and African American groups, and the second among Caucasian and Chinese and Japanese groups, both using Caucasians as the reference group.

To confirm adequacy of adjustment for total fat mass, sensitivity analyses were run limited to African American and Caucasian women in the 2nd and 3rd quartiles of total body fat (quartiles based on the pooled sample of AA and Caucasians) to allow for maximal overlap in total fat mass between the race-ethnic groups. Similarly, analyses were done comparing Caucasian, Chinese, and Japanese women limited to the 2nd and 3rd quartiles of total fat mass (quartiles based on the pooled sample of Chinese, Japanese, and Caucasian women). In addition, data were examined excluding diabetic women and then again after excluding women on menopausal hormone therapy (MHT).

Due to the role of sOB-R in the regulation of circulating leptin levels, we ran additional models comparing race-ethnic differences in leptin levels while further adjusting for sOB-R levels and vice versa to better examine the independent effects of each. In addition, the

interaction between total fat mass and adipokine levels was examined in relation to race-ethnic differences. When significant interactions were found, models were stratified by total fat mass tertiles.

RESULTS

Table 1 compares the anthropometric measures, lifestyle factors, CVD risk factors among the four groups. In unadjusted comparisons, AA women had significantly higher BMI, waist circumference and total body fat compared to Caucasian, Chinese and Japanese women. A higher percentage of AA women reported current smoking and a lower percentage reported a college degree or higher compared to Caucasian, Chinese and Japanese groups. AA women also had lower HDL and triglyceride levels and higher HOMA and CRP levels.

Comparing adipokine levels between the four race-ethnic groups (Table 1), we found that the Caucasian women had significantly higher levels of total and HMW adiponectin compared to both AA and Chinese and Japanese women. Leptin levels were highest and sOB-R levels lowest among AA women, whereas sOB-R levels were similar between Caucasian and Chinese and Japanese women despite Caucasian women having significantly higher BMI and total body fat mass. Adipokine levels did not differ significantly between Chinese and Japanese women.

Generally, the direction and strength of associations between adipokines and different measures of adiposity were similar within each race-ethnic group (Table 2). The exceptions to this were that AA women showed weaker associations between adiposity measures and both adiponectin and HMW adiponectin compared to the other race-ethnic groups. Although unadjusted correlations between adiponectin measures and fat-free mass were negative, the expected positive correlation emerged after adjustment for BMI or fat mass (data not shown).

Comparing adipokine levels between Caucasian and AA women after adjusting for age, study site, education, smoking, physical activity, menopause status and total fat mass, AA women had lower total adiponectin and HMW adiponectin levels (Table 3). The estimates did not change significantly when adjusted for waist circumference (as a proxy for central adiposity) instead of total fat mass. In models comparing leptin levels between the two race/ethnic groups, adjusting for the above stated variables, AA women had higher leptin levels and lower sOB-R levels when either total fat mass or waist circumference were used as the measure of adiposity. Adding HOMA or CRP to the model did not affect the beta estimates significantly.

Interestingly, similar to AA women, compared to Caucasians, Chinese and Japanese women also had significantly lower total adiponectin and HMW adiponectin levels (Table 4). Again, estimates were similar after accounting for different measures of adiposity. In contrast, there were no significant differences in leptin levels between the three groups when models were adjusted for total body fat, but both Chinese and Japanese women had significantly lower leptin levels when models were adjusted for waist circumference instead of total body fat. Both Chinese and Japanese women had lower sOB-R levels compared to Caucasian women after adjusting for the above stated variables including total fat mass or waist circumference.

We found significant effect modification of Caucasian-AA differences in total and HMW adiponectin, as well as sOB-R, by fat mass. We found similar effect modification by fat mass on Caucasian-(Chinese/Japanese) differences in HMW adiponectin and sOB-R. To gain better insight into the nature of this effect modification by fat mass, we stratified regression models by fat mass tertiles and, for both sets of comparisons, we found larger race-ethnic differences at lower fat mass tertiles than at higher fat mass tertiles (Table 5).

We found that in the lowest fat mass tertile, compared to Caucasian women, AA women had significantly lower total and HMW adiponectin levels and lower sOB-R levels, whereas among women in the highest fat mass tertile, differences between the two race-ethnic groups were smaller and in all but the case of Caucasian-AA differences in HMW adiponectin, not statistically significant. Similar patterns were noted when comparing differences between Caucasian and Asian groups. Sensitivity analyses maximizing the overlap in fat mass between any two race-ethnic groups by limiting data to the 2nd and 3rd quartiles of body fat mass, did not alter the beta estimates significantly for either adipokine or sOB-R (data not shown). Similarly, neither adding insulin instead of HOMA to the models, nor excluding women with diagnosed diabetes or on menopausal hormone therapy (MHT) altered the beta estimates in our cohort (data not shown). In addition, the magnitude of differences in leptin levels were similar even after additional adjustment for sOB-R [AA: 2.85 (CI: 0.97, 4.74; p: 0.003); Chinese: -2.23 (CI: -4.93, 0.46; p: 0.104); Japanese: -0.15 (CI: -2.36, 2.65; p: 0.909)], as were differences in sOB-R levels after adjusting for leptin (AA: -0.06 (CI: -0.10, -0.02; p: 0.001); Chinese: -0.14 (CI: -0.21, -0.07; p: <0.001); Japanese: -0.09 (CI: -0.15, -0.02; p: 0.009)].

DISCUSSION

Our study reveals many significant race-ethnic differences in levels of protective and putative adipokines that persist even after adjusting for adiposity using total fat mass or waist circumference. These differences were most apparent in total and HMW adiponectin levels where Caucasians had higher levels as compared to both AA and Chinese and Japanese women. In comparison to Caucasian women, AA women also had significantly higher leptin and lower sOB-R levels, whereas Chinese and Japanese women had similar leptin levels but lower sOB-R levels.

Although previous studies report differences in adipose tissue distribution [35, 36] and inflammatory markers [37–39] between AA and Caucasian groups, race differences in adipokine levels have only recently been reported.[36, 40–42] Similar to our results, Cohen *et al* report an interaction between degree of adiposity and adiponectin levels, where obese Caucasian and AA women show less discrepancy in adiponectin levels compared to women at lower BMIs.[41] Hyatt *et al* report that at any BMI, AA women have lower intra-abdominal adipose tissue, higher levels of inflammatory markers and lower levels of adiponectin compared to Caucasian women.[36] And, Hulver *et al* report significantly lower levels of adiponectin in non-obese AA women compared to non-obese Caucasian women.[40] In the Dallas Heart Study, Turer *et al* found that AA women have lower levels of adiponectin for a given BMI.[43] Our results adjusting for total fat mass corroborate these BMI-adjusted findings. In addition, we show that despite adjusting for waist circumference, as a proxy for central obesity, the differences in adiponectin levels persist, suggesting that adipose tissue distribution does not completely address these racial differences in the secretory profile of adipose tissue. In addition excluding subjects with diabetes and adjusting for insulin resistance and systemic inflammation, each of which may initiate changes in adipokines, did not change our estimates significantly. Whether adipokine differences contribute to the differences in CVD morbidity between the two groups remains to be evaluated.

Although differences in leptin levels were less substantial than adiponectin differences, AA women had higher leptin levels and lower sOB-R levels compared to Caucasian women, even after accounting for differences in total fat mass, and in stratified analyses where associations were looked at only among women with low fat mass, and again only among women with high fat mass. Contradictory to our findings, in a small group of post-menopausal obese women, Nicklas *et al* found that after adjusting for adipose tissue mass,

AA women had significantly lower leptin levels compared to Caucasian women.[44] However, we did not observe these differences even after stratifying our data by menopausal status (data not shown). To our knowledge, this study is the first to document differences in sOB-R levels between AA and Caucasian women. As sOB-R serves to sequester leptin from productive interactions with its signaling receptor,[45] low levels in AA women could add to their CVD risk. We also found that race-ethnic differences in leptin levels were independent of sOB-R levels, thus there may be other mechanisms at play affecting leptin activity and apparent race-ethnic differences in leptin.

Contrary to our expectations, despite a lesser degree of obesity, as seen by lower BMIs, smaller waist circumferences, and less fat mass, compared to Caucasian women, both Chinese and Japanese women also had lower total and HMW adiponectin levels. And despite no differences in fat mass-adjusted leptin levels, they had significantly lower sOB-R levels. Differences were noted in leptin levels when adjusting for central adiposity using waist circumference. It is known that Asian Americans, especially Japanese have high rates of type 2 diabetes despite correspondingly low rates of obesity.[46] These findings have been attributed to differences in adipose tissue distribution between Caucasian and Asian groups. In a large cohort study, Lear *et al*/report greater amounts of total and visceral abdominal adipose tissue in Chinese compared to Caucasian adults even after adjusting for BMI.[47] We found few studies comparing adipokine levels between the two groups. Araneta *et al*/report that at similar BMI, waist circumference and total body fat, Filipina women had lower adiponectin levels than Caucasian women.[48] Interestingly, Conroy *et al* found a differential effect of obesity on adipokine levels between premenopausal Caucasian and Chinese and Japanese women. Whereas overweight and obese Asian women had lower levels of adiponectin and leptin compared to Caucasian women, normal weight Asian women had lower levels of adiponectin but similar levels of leptin.[49] We too, document lower total and HMW adiponectin levels and lower sOB-R levels among our Chinese and Japanese women. However, in contrast to Conroy *et al*'s findings, we found that these differences in adipokine levels diminished with increasing fat mass. The difference in menopausal status between the two cohorts may play a role in the discrepancy of findings. Studies examining changes in adipokine levels across the menopausal transition have yielded contradictory findings, [50–52] and none have examined the race-ethnic differences in adipokine levels during the menopausal transition. Further research is required in this important area to ascertain the role of menopause in race-ethnic differences.

The reasons for these race-ethnic differences in adipokine levels despite adjusting for fat mass remain poorly understood. Differences in adipose tissue distribution may play a role, as visceral and subcutaneous adipose tissue have different adipokine secretory profiles.[53] However, adjustment for waist circumference in our models, though not a perfect proxy for abdominal adipose tissue, had minimal effect on the estimates, suggesting that adjustment for visceral adipose tissue may not completely eliminate these differences either. As fat cell size has been implicated in increasing risk of diabetes, [54] it is possible that differences in fat cell size also play a role in differences in adipokine levels. However, to our knowledge race-ethnic differences in fat cell size have not been examined.

Our results should be viewed in light of certain limitations. We used bioimpedance to measure total body fat. Although waist circumference has been used as a surrogate for central adiposity, and we found no changes in effect size by adjusting for waist circumference in our sensitivity analyses, we recognize that a direct measure of abdominal visceral and subcutaneous adipose tissue would give more precise associations. Due to extreme differences in adiposity and total body fat, we could not directly compare AA and Chinese and Japanese groups. Although other studies have done so after adjusting for fat mass, they were designed to include women with similar body mass indices.[48]

Despite these limitations, by studying differences in adipokine levels in a large, multi-ethnic, multi-center cohort, our results are applicable to midlife women of our target ethnic groups. By adjusting for a direct measure of total fat mass instead of the clinically used BMI, we were able to examine differences in protective and putative adipokine levels among the race/ethnic groups taking into account their actual adiposity. Also, finding similar results using first and second generation adipokines improves the validity of our findings. Thus it appears that even after accounting for adiposity and in analyses limited to non-diabetics, Caucasian women, despite having intermediate levels of adiposity, have significantly higher levels of protective adipokines compared to their AA and Chinese and Japanese peers. In addition, these findings again suggest that total fat mass and adipokine levels may not be interchangeable in determining CVD risk profiles. Future studies are needed to determine whether these adipokine differences may partially explain the higher CVD morbidity and mortality in African Americans, and the higher predisposition to diabetes in Chinese and Japanese groups.

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Table 1

Characteristics of the Study Sample

	African Americans (AA) (n=535)	Chinese (Ch) (n=175)	Japanese (J) (n=215)	Caucasian (W) (n=951)	Overall P value	AA vs. Ch	AA vs. J	AA vs. W	Ch vs. J	Ch vs. W	J vs. W
Age, years	52.4 (2.6)	52.6 (2.4)	52.9 (2.6)	52.6 (2.8)	0.079						
Current Smokers, n (%)	123 (23)	2 (1)	17 (8)	97 (10)	< 0.001	*	*	*	*	*	*
Education level, n (%)					< 0.001	*	*	*	*	*	*
Less than High School	135 (26)	44 (25)	37 (17)	124 (13)							
Post High School	225 (43)	35 (20)	77 (36)	282 (30)							
College and Higher	167 (32)	96 (55)	101 (47)	542 (57)							
Menopause Status, n (%)					< 0.001	*	*	*	*	*	*
Pre/Early Perimenopausal	179 (33)	56 (32)	79 (37)	299 (31)							
Late Perimenopausal/Postmenopausal/Surgical Menopause	345 (64)	98 (56)	124 (58)	546 (57)							
HRT User	11 (2)	21 (12)	12 (6)	106 (11)							
BMI, kg/m ² [mean (SD)]	32.8 (7.7)	23.6 (4.0)	23.9 (4.3)	28.6 (6.9)	< 0.001	*	*	*	*	*	*
Waist circumference, cm [mean (SD)]	97.6 (16.0)	79.1 (10.4)	75.9 (9.7)	89.0 (16.5)	< 0.001	*	*	*	*	*	*
Total Body Fat, kg [mean (SD)]	38.2 (13.3)	19.2 (6.9)	19.4 (7.3)	30.4 (12.9)	< 0.001	*	*	*	*	*	*
Percent Body Fat, % [mean (SD)]	42.7 (6.4)	31.8 (5.9)	32.0 (5.8)	38.1 (7.5)	< 0.001	*	*	*	*	*	*
Fat Free Mass, kg [mean (SD)]	49.1 (8.0)	39.7 (4.7)	39.7 (4.3)	46.4 (6.9)	< 0.001	*	*	*	*	*	*
SBP, mmHg [mean (SD)]	128 (19)	112 (14)	115 (15)	114 (14)	< 0.001	*	*	*	*	*	*
HDL, mg/dL [mean (SD)]	56 (15)	61 (13)	62 (15)	58.4 (15.2)	< 0.001	*	*	*	*	*	*
Triglycerides, mg/dL [Median (IQR)]	102 (57)	113 (72)	116 (75)	113 (78)	< 0.001	*	*	*	*	*	*
Insulin, uIU/mL [Median (IQR)]	12.9 (9.8)	9.0 (4.6)	8.2 (4.5)	9.9 (7.1)	< 0.001	*	*	*	*	*	*
Glucose, mg/dL [Median (IQR)]	89.0 (18)	88.0 (14)	90.0 (12)	86.0 (12)	< 0.001	*	*	*	*	*	*
HOMA-IR [Median (IQR)]	2.9 (2.6)	2.0 (1.2)	1.8 (1.2)	2.1 (1.7)	< 0.001	*	*	*	*	*	*
Hs-CRP, mg/dL [Median (IQR)]	3.7 (6.3)	0.8 (1.5)	0.6 (1.1)	1.8 (3.5)	< 0.001	*	*	*	*	*	*
Adiponectin, µg/ml [mean (SD)]	10.4 (5.7)	12.4 (6.6)	11.7 (5.4)	15.2 (7.5)	< 0.001	*	*	*	*	*	*
HMWA diponectin, µg/ml [Median(IQR)]	3.3 (3.6)	5.7 (6.9)	5.0 (6.1)	7.3 (6.7)	< 0.001	*	*	*	*	*	*
Leptin, ng/ml [mean (SD)]	41.3 (25.5)	14.0 (9.4)	13.9(10.4)	28.3 (21.6)	< 0.001	*	*	*	*	*	*
Soluble Leptin Receptor, ng/ml [Median (IQR)]	26.7 (10.7)	29.8 (13.6)	31.7 (14.5)	30.6 (12.8)	< 0.001	*	*	*	*	*	*

BMI: Body Mass Index; SBP: Systolic Blood Pressure; HDL: High Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; Hs-CRP: High sensitivity C- reactive protein.

Symbols indicate significant differences between the following race-ethnic groups:

* $p < 0.05$ between the race-ethnic groups stated in columns

Table 2

Spearman's Correlations (p-values) of Adipokines with Measures of Adiposity *

	Adiponectin μg/ml	HMW Adiponectin μg/ml	Leptin ng/ml	Soluble Leptin Receptor ng/ml
Caucasian				
BMI, kg/m ²	-0.32	-0.30	0.77	-0.38
Waist circumference, cm	-0.39	-0.37	0.72	-0.40
Total Body Fat, kg	-0.33	-0.32	0.78	-0.38
Percent Body Fat, %	-0.35	-0.32	0.74	-0.38
Fat Free Mass, kg	-0.23	-0.25	0.56	-0.32
African American				
BMI, kg/m ²	-0.16	-0.18	0.70	-0.21
Waist circumference, cm	-0.23	-0.24	0.62	-0.16
Total Body Fat, kg	-0.15	-0.17	0.70	-0.15
Percent Body Fat, %	-0.17	-0.18	0.62	-0.12
Fat Free Mass, kg	-0.09	-0.11	0.51	-0.19
Chinese				
BMI, kg/m ²	-0.30	-0.21	0.72	-0.25
Waist circumference, cm	-0.32	-0.21	0.69	-0.26
Total Body Fat, kg	-0.31	-0.24	0.79	-0.27
Percent Body Fat, %	-0.30	-0.24	0.77	-0.25
Fat Free Mass, kg	-0.23	-0.19	0.43	-0.25
Japanese				
BMI, kg/m ²	-0.36	-0.31	0.80	-0.36
Waist circumference, cm	-0.42	-0.35	0.77	-0.39
Total Body Fat, kg	-0.36	-0.33	0.83	-0.40
Percent Body Fat, %	-0.39	-0.36	0.80	-0.41
Fat Free Mass, kg	-0.26	-0.24	0.53	-0.31

* All correlation coefficients were statistically significant (p<0.01)

Table 3

Multivariable-Adjusted Linear Regression Estimates (95% CI) of Adipokines for Caucasians vs. African Americans.

	Adiponectin, $\mu\text{g/ml}$	HMW Adiponectin, $\mu\text{g/ml}$ *	Leptin, ng/ml	Soluble Leptin Receptor, ng/ml *
Model 1: adjusted for age, total body fat, smoking, physical activity and menopause status, site and education				
Caucasians	Reference	Reference	Reference	Reference
African Americans	-3.40 (-4.29,-2.52)	-0.53 (-0.64,-0.43)	3.26 (1.36, 5.16)	-0.07 (-0.11,-0.03)
	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Model 2: adjusted for age, waist circumference, smoking, physical activity, menopause status and site and education				
Caucasians	Reference	Reference	Reference	Reference
African Americans	-3.32 (-4.15,-2.49)	-0.53 (-0.62,-0.43)	5.29 (3.18,7.40)	0.08 (-0.12,-0.04)
	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Model 3: Model 1+HOMA				
Caucasians	Reference	Reference	Reference	Reference
African Americans	-3.45 (-4.35,-2.55)	-0.53 (-0.64,-0.43)	3.40 (1.45,5.35)	-0.07 (-0.11,-0.03)
	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Model 4: Model 1+CRP				
Caucasians	Reference	Reference	Reference	Reference
African Americans	-3.26 (-4.15,-2.38)	-0.51 (-0.61,-0.41)	3.10 (1.19,5.01)	-0.07 (-0.11,-0.03)
	p < 0.001	p < 0.001	p = 0.001	p < 0.001

* log transformed.

Table 4

Multivariable-Adjusted Linear Regression Estimates (95% CI) of Adipokines for Caucasians vs. Asians.

	Adiponectin, $\mu\text{g/ml}$	HMW Adiponectin, $\mu\text{g/ml}^*$	Leptin, ng/ml	Soluble Leptin Receptor, ng/ml^*
Model 1: adjusted for age, total body fat, smoking, physical activity, menopause status, site and education				
Caucasians	Reference	Reference	Reference	Reference
Chinese	-5.50 (-7.07, -3.93)	-0.57 (-0.75, -0.38)	-1.55 (-4.25, 1.15)	-0.13 (-0.20, -0.06)
	p < 0.001	p < 0.001	p: 0.259	p < 0.001
Japanese	-5.48 (-6.95, -4.02)	-0.61 (-0.78, -0.44)	0.59 (-1.92, 3.11)	-0.09 (-0.15, -0.02)
	p < 0.001	p < 0.001	p: 0.643	p: 0.008
Model 2: adjusted for age, waist circumference, smoking, physical activity, menopause status, site and education				
Caucasians	Reference	Reference	Reference	Reference
Chinese	-5.57 (-7.07, -4.07)	-0.57 (-0.75, -0.40)	-4.76 (-7.73, -1.78)	-0.13 (-0.19, -0.06)
	p < 0.001	p < 0.001	p: 0.002	p < 0.001
Japanese	-4.93 (-6.28, -3.58)	-0.55 (-0.71, -0.39)	-2.86 (-5.54, -0.18)	-0.07 (-0.13, -0.01)
	p < 0.001	p < 0.001	p: 0.037	p < 0.001
Model 3: Model 1 + HOMA				
Caucasians	Reference	Reference	Reference	Reference
Chinese	-5.32 (-6.91, -3.74)	-0.54 (-0.72, -0.35)	-1.72 (-4.47, 1.03)	-0.13 (-0.20, -0.06)
	p < 0.001	p < 0.001	p: 0.220	p < 0.001
Japanese	-5.61 (-7.08, -4.14)	-0.63 (-0.80, -0.45)	0.69 (-1.86, 3.23)	-0.10 (-0.16, -0.04)
	p < 0.001	p < 0.001	p: 0.597	p < 0.001
Model 4: Model 1 + CRP				
Caucasians	Reference	Reference	Reference	Reference
Chinese	-5.59 (-7.16, -4.02)	-0.58 (-0.77, -0.40)	-1.51 (-4.22, 1.20)	-0.13 (-0.20, -0.07)
	p < 0.001	p < 0.001	p= 0.275	p < 0.001
Japanese	-5.64 (-7.10, -4.18)	-0.63 (-0.80, -0.46)	0.69 (-1.83, 3.22)	-0.09 (-0.16, -0.03)
	p < 0.001	p < 0.001	p= 0.590	p= 0.005

*
log transformed.

Table 5

Multivariable-Adjusted Linear Regression Estimates (95% CI) of Adipokines Among Race-Ethnic Groups by Fat Mass Tertiles.*

		HMW Adiponectin, $\mu\text{g/ml}^\dagger$			Soluble Leptin Receptor, $\text{ng/ml}^\dagger$		
		Lowest Fat Mass Tertile (7.0–21.9 kg) N=579	Intermediate Fat Mass Tertile (22.0–33.8 kg) N=579	Highest Fat Mass Tertile (33.9–84.5 kg) N=578	Lowest Fat Mass Tertile (7.0–21.9 kg) N=579	Intermediate Fat Mass Tertile (22.0–33.8 kg) N=579	Highest Fat Mass Tertile (33.9–84.5 kg) N=578
Caucasian and African American Comparisons							
Caucasians	Reference	Reference	Reference	Reference	Reference	Reference	Reference
African	–0.63	–0.58	–0.44	–0.17	–0.07	–0.04	–0.10
Americans	(–0.91, –0.34)	(–0.74, –0.42)	(–0.60, –0.28)	(–0.28, –0.06)	(–0.13, –0.01)	(–0.10, 0.02)	(–0.10, 0.02)
	$p < 0.001$	< 0.001	$p < 0.001$	$p < 0.003$	0.028	$p < 0.164$	
Caucasian and Asian Comparisons							
Caucasians	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Chinese	–0.50	–0.97	–0.10	–0.13	–0.27	0.10	–0.10
	(–0.76, –0.25)	(–1.31, –0.63)	(–0.66, –0.47)	(–0.22, –0.03)	(–0.40, –0.14)	(–0.11, 0.30)	(–0.11, 0.30)
	$p < 0.001$	$p < 0.001$	$p < 0.739$	$p < 0.010$	$p < 0.001$	$p < 0.343$	
Japanese	–0.51	–1.05	–0.23	–0.07	–0.23	–0.08	–0.08
	(–0.74, –0.28)	(–1.35, –0.75)	(–0.84, 0.39)	(–0.16, 0.02)	(–0.34, –0.11)	(–0.30, 0.14)	(–0.30, 0.14)
	$p < 0.001$	$p < 0.001$	$p < 0.469$	$p < 0.112$	$p < 0.001$	$p < 0.475$	

* Models adjusted for age, smoking, physical activity, menopause status, site and education and total body fat tertiles

† log-transformed