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Sex and race differences in the prevalence of Fatty Liver Disease as measured by CT liver attenuation in European American and African American participants of the NHLBI Family Heart Study

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Abstract

Liver attenuation (LA) (Hounsfield Units, HU) by computed tomography (CT) is a validated quantitative measure inversely related to liver fat burden. We examined race-and sex- differences on the distribution of LA (one of the first stages of fatty liver disease) and the predictors of these mean differences in European American (EA) and African American (AA) participants of the Family Heart Study. A total of 1242 (1064 EA, 178 AA) and 1477 (1150 EA, 327 AA) men and women, respectively, underwent CT examination from which LA and abdominal adipose volume were measured. LA (adjusted for phantom and field center) was the dependent variable in linear mixed models (to control for family relatedness) that tested for mean differences by race and by sex. Independent explanatory variables included age, body mass index, visceral adipose tissue volume, subcutaneous adipose tissue volume, alcohol consumption, TG, HDL-C, and insulin resistance. Mean LA varied significantly by sex, [(men) 57.76 ±10.03 HU and (women) 60.03 ±10.91 HU, p=0.0002], but not by race. Higher LA was associated with older age, while higher values of VAT, triglycerides, and insulin resistance were associated with lower LA in men and women. In contrast, alcohol consumption and BMI were associated with lower LA only among men. In analyses stratified by race LA was associated with alcohol consumption, VAT, and insulin resistance in both EA and AA and with age, BMI, and HDL-C in EA participants only. Our study findings confirm that there are important sex differences and race by sex interaction effects on the distribution of liver attenuation, the prevalence of FLD, and on the influence of metabolic risk factors on LA and FLD.

INTRODUCTION

Fatty liver disease (FLD) is characterized by increased intrahepatic triglyceride (TG) content with or without inflammation and fibrosis [1–3] in a liver specimen. Excess fat in the liver (steatosis) is the early stage of FLD, and there is increasing evidence that it is associated

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with insulin resistance and features of the metabolic syndrome, including abdominal fat accumulation, type 2 diabetes (T2D), hypertriglyceridemia, low serum high-density lipoprotein cholesterol (HDL-C) concentrations, and hypertension [1–2, 4–9]. Although it is thought that steatosis is very common in the population, the exact prevalence of FLD is largely unknown, as estimates are highly dependent on the diagnostic criteria implemented.

Steatosis and fibrosis can occur in individuals that are asymptomatic. An indirect assessment of liver fat in asymptomatic, population-based samples is now possible with the use of computed tomography (CT) scans. Liver attenuation (LA) is measured from CT scans and is a validated measure of liver fat [10]. This measure is rapidly becoming an important noninvasive surrogate of histologically diagnosed FLD [11], where lower values of LA are associated with increasingly fatty liver content. Of the several CT criteria of FLT investigated, a LA value of ≤ 40 has been shown to best correlate with a pathologic fat content of ≥ 30%, indicating moderate-to-severe-steatosis [11]. Complicating these assessments is the distinction between FLD and the more widely studied non alcoholic fatty liver disease (NAFLD), which is not well defined. Indeed several different definitions of NAFLD have been applied in the literature, with some studies excluding only those individuals with excessive alcohol consumption (> 42 drinks/week for men and >28 drinks/wk for women) and other studies using a strict and more widely applied exclusion of all those individuals that consume alcohol above the recommended level (> 14 drinks/week for men and >7 drinks/week for women).

Largely because of the many diagnostic criteria and the lack of availability of CT assessed liver fat in population-based samples, the epidemiology of fatty liver is not well-characterized. However, in several population-based samples that interrogated fatty liver in asymptomatic individuals using either biopsy or CT scan, differences in the prevalence of FLD by race and gender [12–14] were noted. Yet no studies have examined race and sex differences in liver fat and their possible differential associations with risk and lifestyle factors. The purpose of this study was to examine the distribution of LA in a population-based study of cardiovascular disease, the NHLBI Family Heart Study (FHS). Of particular interest was the difference in the distribution of LA by race and sex groups and an examination of whether these differences could be attributed to measured risk and lifestyle factors in European American (EA) and African American (AA) individuals.

MATERIALS and METHODS

Study Population

The FHS is a multicenter, population-based, family study designed to investigate the determinants of cardiovascular disease [15]. Families in the FHS were selected at random (588 families) or ascertained for family history of CHD (656 families) using information collected in the parent studies, which were the Framingham Heart Study (Framingham, MA, USA), the Utah Health Family Tree Study (Salt Lake City, UT, USA) or the Atherosclerosis Risk in Communities Study (Minneapolis Suburbs, MN, USA and Forsyth County, NC, USA). Between 2002 and 2003 about two-thirds of the families (largest families available who also had microsatellite markers typed by the Mammalian Genotyping Service for linkage studies) of the FHS were invited to participate in a follow-up clinical examination that included measurement of calcified coronary and aortic plaque calcification with cardiac computed tomography (CT) using standardized procedures and quality control methods developed in NHLBI's MESA and CARDIA studies [15]. In addition to the original FHS study centers, 631 African–American subjects participating in the Hypertension Genetic Epidemiology Study (HyperGEN) were recruited from the University of Alabama field center.

CT Scan Related Phenotypes

Participants underwent a cardiac multi-detector CT (MDCT) exam with four detectors using a standardized protocol as described previously [16]. For participants weighing 100 kg (220 lbs) or greater, the mAs were increased by 25%. The effective radiation exposure for the average participant of each coronary scan was 1.5 mSv for men and 1.9 mSv for women. Participants received two sequential scans. CT images from all study centers were sent electronically to the central CT reading center located at Wake Forest University Health Sciences, Winston Salem, NC, USA.

Liver Attenuation (LA)—Two cardiac gated images of the thorax were obtained which include the upper third of the liver. Hepatic attenuation was measured by placing three round regions of interest (ROI's) in two slices of the superior right lobe of the liver. The first scan was used unless the breath-hold depth or other artifact required use of the second scan. The 6 ROI values (3 from each scan) are then averaged as a mean LA. In a pilot study, we demonstrated high intra-class correlation (>0.95) of ROI's throughout the liver with the exceptions of the regions of the *porta hepatis* and caudate lobe. In addition, intra-reader correlation (>0.95) between repeat analyses of the same liver regions was achieved. As part of the FHS-SCAN CT protocol all participants were imaged with a standardized phantom that contains material that simulates water (expected HU=0) as well as increasing densities of calcium (50, 100 and 200 mg of calcium). These concurrent phantom measures at water density were used to adjust and standardize the liver attenuation measurements. Lower values of LA indicate higher fat content. Moderate-to-severe hepatic steatosis is generally defined as ≤ 40HU [11].

Adiposity Depots in the Abdomen—CT scans of the abdominal aorta were performed helically with 2.5 mm collimation, with a field of view (FOV) of 35 cm, centered on the abdominal aorta, and reconstructed at a FOV of 50 cm to include the whole abdomen. Segments of fat depots in the abdomen were measured for fat mass using a three dimensional volumetric approach to determine volume of adipose tissue in cm^3 [17]. Experienced analysts measured total abdominal adipose tissue volume, as well as the fat visceral adipose tissue volume (VAT), and subcutaneous adipose tissue volume (SAT) depots using the well established range of attenuation between −190 to −30 Hounsfield units to define adipose tissue. Measurements of fat volume were performed with a GE Advantage Workstation 4.2 using the Volume Analysis software (General Electric Medical Systems, Waukesha, WI). Two approaches were employed: 1) A volume centered based the lumbar spine at the L4–L5 level measuring 12.5 mm in length along the z-axis which is directly comparable to previous single slice techniques reported in the literature and 2) A volume starting from sacrum and extending cephalad for 150 mm, to provide a more comprehensive coverage of the abdominal adipose tissue irrespective of level of measurement. The measurements from both slices were averaged together for each adipose depot volume.

Other Variables

Biochemical Measures—TG levels were measured by a Roche COBAS FARA centrifugal analyzer (Boehringer Mannheim Corp., Indianapolis, IN 46250-0457). HDL-C was determined after precipitation of other lipoprotein fraction by dextran sulfate[18]. Fasting serum glucose was measured on a clinicalchemistry slide (EKTACHEM; Eastman Kodak Co, Rochester, NY). Fasting insulin was measured by the coated-tube RIA method distributed by Diagnostic Products Corporation (Los Angeles, CA 90045). HOMA-IR was calculated as the product of fasting insulin (in μ units per milliliter) and fasting glucose (in milligrams per deciliter) divided by 405 [19]. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). Because excessive alcohol use is associated with elevated ALT, participants were asked about the number of 1.5-oz

cocktails, 12-oz glasses (or cans) of beer, and 4-oz glasses of wine they consumed by day and in 1 week. Total alcohol intake in grams per day was calculated from the reported intakes of beer, wine, and spirits. We excluded six women and ten men who reported excessive alcohol consumption (> 42 drinks/week for men and >28 drinks/wk for women) regardless of their LA value, so as to avoid participants that had fatty liver consistent with alcoholic liver disease [20]. We also ran models with and without individuals who reported alcohol consumption above the recommended level (> 14 drinks/week for men and >7 drinks/week for women) so as to assess the most strict definition of non alcoholic fatty liver disease (NAFLD). This resulted in an additional exclusion of 145 men (EA = 121, AA = 24) and 168 women (EA = 137, AA = 31). While alcohol consumption was associated with LA in men the adjustment for alcohol consumption did not change the estimates for the other explanatory variables. Alcohol intake was not associated with LA in women with and without the exclusion criteria for limiting drinks to 7 per week. Therefore, all models will only exclude individuals with excessive alcohol consumption (N = 16) and alcohol drinking will be accounted for as a covariate effect.

Application to FHS Data

Informed consent was obtained from all participants, and this project was approved by the Institutional Review Boards of all participating institutions. Our initial sample size included 1554 (1236 EA, 218 AA) men and 1935 (1520 EA, 415 AA) women. Complete phenotypic data and alcohol limits below excessive amounts (defined above) were available on a total of 1242 (1068 EA, 178 AA) men and 1477 (1150 EA, 327 AA) women. Most excluded individuals were missing information on alcohol intake (80 AA, 335 EA women, and 136 EA, 32 AA men). There were no differences in LA by sex or race among individuals missing alcohol intake or other explanatory phenotypic data. In EA women missing information about alcohol intake, HDLC was lower than in those with information (52.1±0.8 versus 54.8±0.4, p=0.003, respectively).

Statistical Methods—We first obtained residuals from linear regression analysis of LA on the CT calibration phantom and performing field center. Using linear mixed models (to control for family relatedness), we regressed LA residuals on independent explanatory variables of age, BMI, visceral adipose tissue volume (VAT), subcutaneous adipose tissue volume (SAT), alcohol consumption, TG concentration, and insulin resistance (HOMA-IR).

We explored interactions between each independent variable with race, and sex. We then stratified models by race and/or sex and compared parameter estimates between models within strata using t-tests. We used t-tests for comparison of means (or parameter estimates, β) between groups A and B is: $(\beta A - \beta B)/SQRT[(SE A)^2 * DF A + (SE B)^2 * DF B)/(DF A + DF B)]$, where DF (degree of freedom) = number of subjects − number of families − 2, and SE = standard error. The significance level (p value) is based on two-tailed T test.

RESULTS

Characteristics of study participants

Descriptive statistics of the study participants are reported in Table 1. AA participants were younger and more likely to be female than EA participants. AA participants had higher BMI, HOMA-IR, and HDL-C, but lower TG and VAT than EA participants. Alcohol consumption and mean serum ALT levels were highest among AA men, intermediate among EA men, and lowest among women. Patterns of intra-abdominal tissue volume differed among sex and race strata. Men had more VAT but less SAT than women. VAT was higher in EA than AA participants, while SAT was greater in AA than EA participants. Abdominal adipose tissue volume was greatest in AA women, intermediate in EA men and women, and

lowest in AA men. Mean LA varied significantly by sex, [(men) 57.76 ±11.02 HU and (women) 60.33 ±10.62 HU, p=0.0002], but not by race. Moderate to severe hepatic steatosis, as defined by LA< 40 HU, was observed in 5.1% of AA men, 7.4% of EA men, 4.6% of AA women and 6.5% of EA women. The lower prevalence of liver attenuation among women persisted across subgroups of VAT and HOMA-IR (data not shown).

Association between LA and Risk Factor Profiles, by Sex

Univariate associations between the continuous measure of LA and participant anthropometric, metabolic, and CT measures stratified by sex are shown in Table 2. Higher age was associated with higher LA, while higher levels of VAT, TG, and insulin resistance were associated with lower LA in men and women. We noted that the association of LA with VAT and HOMA-IR had a stronger magnitude of effect in women (all P values 0.01 to <0.0001). Alcohol consumption and BMI were associated with lower LA only among men.

Association between LA and Risk Factor Profiles, by Race

Univariate associations between the continuous measure of LA and participant anthropometric, metabolic, and CT measures, stratified by race are shown in Table 3. Alcohol consumption, VAT, and insulin resistance were associated with lower LA in both ethnic groups. BMI, HDL-C, and TG were significantly associated with lower LA in European participants only. Higher age was significantly associated with higher LA only in white participants (P values 0.01 to <0.0001), and in AA participants the effect estimates were in the same direction, although not significantly associated.

Results for Interaction Model

In multi-variable adjusted regression models, higher levels of alcohol consumption, BMI, VAT, TG, and HOMA-IR were significantly associated with lower LA levels. The multivariable-adjusted p-values for VAT and HDL-C were all non-significant. In adjusted models including interactions (Table 4), we found significant 2-way interactions ($p<0.10$) between race and sex, race and TG, race and HOMA-IR, sex and HOMA-IR, and sex and BMI. There was also evidence for a 3-way interaction between race, sex, and HOMA-IR (P for interaction = 0.0002).

DISCUSSION

LA, as measured from CT scans, is a noninvasive validated measure of liver fat, which captures the initial stages of FLD and NAFLD, in individuals who are asymptomatic. The epidemiology of FLD and NAFLD is largely unexplored, particularly among studies that have measured liver fat non-invasively. Using CT scans, we sought to examine race and sex differences in the distribution of LA in EA and AA participants of the NHLBI Family Heart Study, and to identify the explanatory variables that account for these observed differences.

The prevalence of moderate-to-severe hepatic steatosis as defined by liver attenuation ≤40 HU was 6.6% in the entire sample, ranging from 3.9% in AA women to 8.5% in EA men. The population prevalence reported here is similar to that reported by Boyce [12] in 3,357 asymptomatic United States adults, also assessed with CT scan. Higher prevalence figures for fatty liver disease have been reported in the literature, in clinical and hospital-based studies ascertained for liver disease, and in population based studies that used CT scans and the ratio of attenuation in the liver to spleen, as an assessment of fatty liver disease.

In agreement with some other community-based studies, we found a higher prevalence of steatosis among EA compared to AA, and among men in comparison to women [1, 13, 21]. However, whereas several previous studies have reported a higher prevalence of FLD and

NAFLD among EA participants in comparison to AA participants, only one previous study reported a higher prevalence of FLD among men, and this was restricted to the EA participants only [13]. Our study findings are notable here for several reasons. First of all, our study is the first to demonstrate a sex difference in a population of AA descent. Moreover, our study found important sex-by-race interaction effects on the distribution of LA which may explain why previous studies have not reported important sex effects. Our study findings are suggestive of important race and sex differences in the accumulation of liver fat during the early stages of FLD and NAFLD. This suggests that race and sex effects may be important during the early pre-clinical stages of liver fat accumulation, rather than the result of long term inflammation that occurs after acute liver damage has begun.

We hypothesized that the observed differences in LA by race and sex were due to the differences in the effects of risk factors for FLD. In general, we found support for this hypothesis in that age, alcohol consumption and VAT were independent correlates of LA across all race and sex strata. In contrast, the associations between insulin resistance and BMI with LA differed among race and sex strata. Higher age was associated with higher liver fat which at first may seem counter-intuitive, although a similar relationship was observed by Wagenknecht and colleagues in the IRAS family study [22]. We observed a lower TG and adipose tissue volume in participants who were older than 60 years as compared to those who were younger than 60 years and this may suggest an age-dependent loss in fat and muscle mass. Certainly such a wasting phenomenon is well supported by the clinical and epidemiological literature [23].

VAT and insulin resistance have been reported to be the strongest predictors of FLD in EA, AA, and Hispanic American (HA) individuals [22, 24]. We found that insulin resistance and VAT were important predictors in both EA and AA men and women. In the IRAS study, age, TG, and PAI-1 were additional correlates of NAFLD in Hispanics, while serum adiponectin was an independent predictor only in AA. Together these findings reinforce the relationship between FLD and features of the metabolic syndrome (abdominal adiposity and insulin resistance) [1–2, 6] relative to overall adiposity measures such as BMI, but also suggest the etiology of FLD may differ between ethnicities.

BMI displayed a strong inverse association with LA primarily in EA participants. Additionally, this effect was more pronounced in males. This stronger pattern of association in EA participants was apparent even though BMI levels were much higher in African American participants. Overall, it is apparent that LA is strongly influenced by the location and possibly by the metabolic activity of fat depots, more so than overall adiposity or body size. Indeed, VAT was an important predictor in all race and sex strata whereas the effect of BMI was limited.

The lower prevalence of FLD among AA individuals is unanticipated in light of this population's reported higher levels of ALT, total body, and subcutaneous adipose tissue volume, insulin resistance, and alcohol consumption, compared to EA. In the Dallas Heart Study, controlling for intraperitoneal fat content almost entirely eliminated racial differences in fatty liver [25] In contrast, insulin resistance remained higher and TG levels lower in AA after adjustment for intraperitoneal fat. We found similar results in our study. Controlling for visceral fat (adjusted for BMI) minimized racial difference in LA between AA and EA, while insulin resistance was higher and TG lower in AA men and AA women. Therefore, the metabolic response to obesity and/or insulin resistance differs in AA compared to other populations; AA individuals appear to be more resistant to the accumulation of visceral and hepatic fat and therefore its negative impact may be lessened. The association between fatty liver and metabolic traits may be due to particular fat depots such as VAT. The ability to expand SAT in response to increased caloric intake may also be important [26]. In this regard,

AA individuals and women may have a greater ability to expand the lower extremity SAT and thus have less of an effect on VAT and liver fat.

Another possibly more important distinction is that AA individuals have higher HDL-C and lower TG levels than HA or EA with similar levels of IR, and therefore may be relatively protected from the lower HDL-C and higher TG that likely have a large impact on the accumulation of liver fat in EA individuals. In fact, the data from our study are supportive of this hypothesis. In EA subjects from the FHS, fatty liver remained associated with higher TG, lower HDL-C, and insulin resistance, even after controlling for VAT, suggesting the independent roles of different fat depots. HDL-C transports cholesterol away from the arteries and surrounding tissues back to the liver for reuse and/or excretion. The apparent race differences in the prevalence of fatty liver may be related to the fact that HDL-C protects against macrophage damage which can contribute to insulin resistance, inflammation and may exacerbate fatty liver disease[4–6]. HDL-C subfractions have been shown to differ in degrees of protection against oxidative damage [27–28] Race and gender differences in fatty liver disease may be partly explained by any racial variation among genes associated with HDL-C subfractions.[27–33]. In Caucasian men and women, HDL-C levels and molecule size may be partly explained by genetic differences in proteins involved with lipoprotein metabolism [32, 34]. We noted that EA women had slightly lower HDL-C levels compared to AA women.

Although unexplored in this paper, it is also possible that genetic factors contribute to the race differences in susceptibility to FLD. Histologically determined fatty liver has been reported to be moderately heritable in EA, AA, and HA individuals.[2, 13] In our study population, LA is also modestly heritable, with a heritability estimate of 28% recently reported [35]. In addition, allelic variation in patatin-like phospholipase domain containing 3 gene (*PNPLA3*) has been strongly associated with FLD in HA and AA individuals [36]. The *PNPLA3* rs738409 G susceptibility allele is most common in Hispanics, the group most susceptible to FLD. A distinct genetic variant of *PNPLA3* (rs6006460[T]) is associated the lower hepatic fat content in African Americans the group at lowest risk of FLD. Of note, the G susceptibility allele of rs738409 has also been associated with fatty liver disease in EA individuals [35]. Thus, the allelic spectrum and respective frequency differences in *PNPLA3* and perhaps other unidentified genetic variants may contribute to racial differences in susceptibility to FLD. However, a difference in the prevalence of NAFLD across population groups is likely to be influenced by both environmental and genetic risk factors.

This study has several important strengths. First, we used a non invasive and well validated measure of liver attenuation from CT scans with a standardized phantom on a large number of subjects in a population-based study. In addition, these study participants were extensively characterized for multiple metabolic phenotypes of interest, particularly with CT measured adipose tissue volumes as well as parameters of lipid and glucose metabolism. Similar data collected in AA subjects allowed us to investigate race differences in the distribution of LA in EA versus AA participants as well as differences in risk factors that predicted these differences. This study was also able to characterize liver attenuation and thus fatty liver disease in a population based family study, early in the course of disease and prior to the onset of symptoms.

The most notable limitation of our study was the smaller sample size of AA available for study, which may result in reduced power for identifying AA - EA differences in LA that can be attributed to measured risk and life style factors. However, we were cautious in our interpretation of race differences, particularly with respect to non-significant findings in the AA stratum. Another limitation is the possibility of ascertainment bias, as some of the EA families were recruited because of a familial excess of coronary artery disease and the AA

families were recruited from a hypertension study. However, the distribution of LA by family ascertainment status (for CHD versus random) was not significantly different in European American families (all $P > 0.46$) nor was hypertension status significantly associated with LA in African American participants (all $P > 0.32$).

In conclusion, this is one of the first papers to directly investigate race and sex differences in the distribution of a quantitative measure of liver fat, as well as prevalence of steatosis. Consistent with previous studies, we found a higher prevalence of steatosis among EA compared to AA participants in both males and females. In addition, we found a higher prevalence of steatosis among men than among women in both EA and AA descent populations. Our study is the first to confirm this sex difference in AA decent individuals.

This is also one of the first papers to directly interrogate whether observed race and sex differences in the distribution of LA could be attributed to measured risk and lifestyle factors. We found that age, VAT, TG, and insulin resistance were significantly associated with LA in all race and sex strata. Significant differences in LA between males and females could only be attributed to differences in alcohol consumption, BMI, VAT, and insulin resistance. In contrast, significant differences in LA between EA and AA participants were attributed to differences in BMI, TG, and HDL-C.

Liver attenuation appears to frequently co-occur with a typical constellation of metabolic syndrome related traits including insulin resistance, central adiposity, and dyslipidemia. Our findings suggest that there may be fundamental differences in the pathophysiology of fatty liver disease across race-sex groups, with a higher prevalence of fatty liver disease in EA compare to AA and the highest prevalence in EA males. An understanding of the mechanisms responsible for these sex and race differences in the prevalence of NAFLD may lead to improved therapeutic strategies for the prevention and treatment of the potentially serious chronic long-term sequelae of fatty liver disease.

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Table 1

Descriptive Statistics of the Family Heart Study cohort by race and sex

	African American Males, n=178		European American Males, n=1068		African American Females, n=328		European American Females, n=1153	
	Mean or %	**SD**	**Mean or %**	**SD**	**Mean or %**	**SD**	**Mean or %**	**SD**
Liver attenuation, unadjusted (Hounsfield Units, HU)	59.67	9.46	57.47	11.18	59.88	9.04	60.15	11.31
Liver attenuation[1] (HU)	−0.17	9.85	−1.19	10.76	0.28	9.28	0.79	10.84
LA below 40 HU (% yes)	4.49		8.26		4.27		6.20	
Adjusted LA[1] below 40 HU (% yes)	5.06		7.32		4.57		6.52	
Age (yrs)	52.68	10.74	56.88	13.35	54.41	11.17	57.83	13.12
Alcohol (grams/wk)	51.12	85.39	47.12	77.52	16.43	40.38	21.98	41.46
Drinks alcohol (% yes)	43.82		47.00		23.03		35.37	
Body Mass Index (kg/m^2)	30.25	6.04	29.22	4.65	33.94	7.46	28.37	6.25
Abdominal visceral adipose[3] (cm^3)	154.50	78.50	202.90	95.29	134.79	58.07	138.17	76.27
Abdominal subcutaneous adipose[3] (cm^3)	291.10	143.27	247.51	107.15	438.34	165.91	315.16	142.58
Abdominal total adipose[3] (cm^3)	456.66	190.38	467.32	179.90	586.29	201.23	471.00	202.54
Alanine Aminotransferase ALT (IU/L)	28.81	35.27	25.70	19.45	16.59	10.69	18.86	13.01
HOMA-IR[2]	3.21	3.31	2.62	3.00	3.51	3.25	2.12	2.19
Triglycerides (mg/dl)	115.68	87.31	152.26	104.65	111.15	82.12	135.99	84.04
HDL-Cholesterol (mg/dl)	47.31	14.60	42.40	10.86	56.45	14.91	54.84	15.27

[1] Adjusted for phantom and center. A standardized phantom contains material that simulates water (expected HU=0) as well as increasing densities of calcium (50, 100 and 200 mg of calcium). These concurrent phantom measures at water density were used to adjust and standardize the liver attenuation measurements.

[2] HOMA-IR (homeostasis model of insulin resistance)= (fasting serum glucose [mg/L]* fasting serum insulin [mU/L]/405)

[3] Adipose depot volumes are in cm^3 per average of 12.5 mm and 150mm “slices”

Table 2

T-test for beta differences by sex for liver attenuation[1] (in HU)

	Men; N=1242, number of families = 580			Women; N=1477, number of families= 622			T-test for Beta difference by sex			
	Beta	**SE**	**p**	**Beta**	**SE**	**p**	**Beta Difference**	**df_{BD}[3]**	**SE**	**p**
Race (African American)	1.22	0.81		1.16	0.67					
Age (yrs)	0.06	0.02	*	0.08	0.02	*	−0.02	1513	0.022	0.5
Alcohol (grams/wk)	−0.02	0.004	**	−0.01	0.01		−0.01	1513	0.005	*
Body Mass Index (kg/m^2)	−0.54	0.13	**	−0.07	0.09		−0.47	1513	0.108	**
Abdominal visceral adipose (cm^3)	−0.01	0.004	**	−0.03	0.01	**	0.02	1513	0.005	**
Abdominal subcutaneous adipose (cm^3)	0.002	0.005		0.002	0.003					
Triglycerides (mg/dl)	−0.01	0.003	**	−0.02	0.003	**	0.005	1513	0.003	0.1
HDL-Cholesterol (mg/dl)	−0.01	0.03		−0.03	0.02					
HOMA-IR[2]	−0.53	0.08	**	−0.97	0.10	**	0.44	1513	0.09	**

[1] Adjusted for phantom and center. A standardized phantom contains material that simulates water (expected HU=0) as well as increasing densities of calcium (50, 100 and 200 mg of calcium). These concurrent phantom measures at water density were used to adjust and standardize the liver attenuation measurements.

[2] HOMA-IR (homeostasis model of insulin resistance)= (fasting serum glucose [mg/L]* fasting serum insulin [mU/L]/405)

[3] df_{BD} (degrees of freedom for beta difference)= (N − number of families − 2)

** p<0.0001,

* p<0.01,

† p<0.05

Table 3

T-test for beta differences by race for liver attenuation[1] (in HU)

	African Americans; N=505, number of families=204			Caucasians; N=2214, number of families=503			T-test for Beta difference by race			
	Beta	**SE**	**p**	**Beta**	**SE**	**p**	**Beta Difference**	**df_{BD}[3]**	**SE**	**p**
Sex (Male)	−0.13	0.98		0.68	0.56					
Age (yrs)	0.05	0.04		0.07	0.02	**	−0.02	2008	0.022	0.3
Alcohol (grams/wk)	−0.01	0.01	*	−0.02	0.003	**	0.004	2008	0.004	0.4
Body Mass Index (kg/m^2)	0.01	0.13		−0.37	0.08	**	0.38	2008	0.09	**
Abdominal visceral adipose (cm^3)	−0.03	0.01	*	−0.02	0.004	**	−0.01	2008	0.005	0.1
Abdominal subcutaneous adipose (cm^3)	−0.005	0.005		0.005	0.003					
Triglycerides (mg/dl)	−0.003	0.005		−0.02	0.002	**	0.01	2008	0.003	**
HDL-Cholesterol (mg/dl)	0.03	0.03		−0.03	0.02	†	0.06	2008	0.02	*
HOMA-IR[2]	−0.62	0.11	**	−0.80	0.07	**	0.18	2008	0.08	†

[1] Adjusted for phantom and center. A standardized phantom contains material that simulates water (expected HU=0) as well as increasing densities of calcium (50, 100 and 200 mg of calcium). These concurrent phantom measures at water density were used to adjust and standardize the liver attenuation measurements.

[2] HOMA-IR (homeostasis model of insulin resistance)= (fasting serum glucose [mg/L]* fasting serum insulin [mU/L]/405)

[3] df_{BD} (degrees of freedom for beta difference)= (N − number of families − 2)

** p<0.0001,

* p<0.01,

† p<0.05

Table 4

Estimates for full interaction model for liver attenuation[1] (in Hounsfield Units)

	N=2719, number of families = 707		
	Beta	**SE**	**p-value**
Intercept	10.12	1.96	<.0001
Sex (Male)	−2.29	1.03	0.0002
Race (African American)	7.65	2.06	0.03
Age (yrs)	0.07	0.02	<.0001
Alcohol (grams/wk)	−0.02	0.003	<.0001
Body Mass Index (kg/m^2)	−0.14	0.07	0.06
Abdominal visceral adipose (cm^3)	−0.02	0.003	<.0001
Abdominal subcutaneous adipose (cm^3)	0.002	0.003	0.5
Triglycerides (mg/dl)	−0.01	0.002	<.0001
HDL-Cholesterol (mg/dl)	−0.02	0.01	0.12
HOMA-IR[2]	−1.41	0.12	<.0001
Race* Sex (African American*Male)	2.64	1.36	0.05
Body Mass Index (kg/m^2)*Sex (Male)	−0.34	0.07	<.0001
Triglycerides (mg/dl)*Race (African American)	0.009	0.006	0.10
HOMA-IR* Race (African American)	0.82	0.17	<.0001
HOMA-IR* Sex (Male)	0.93	0.14	<.0001
HOMA-IR* Race (African American) *Sex (Male)	−0.98	0.25	0.0001

[1] Adjusted for phantom and center. A standardized phantom contains material that simulates water (expected HU=0) as well as increasing densities of calcium (50, 100 and 200 mg of calcium). These concurrent phantom measures at water density were used to adjust and standardize the liver attenuation measurements.

[2] HOMA-IR (homeostasis model of insulin resistance)= (fasting serum glucose [mg/L]* fasting serum insulin [mU/L]/405)