

# Fatty Liver, Abdominal Visceral Fat, and Cardiometabolic Risk Factors

## The Jackson Heart Study

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**Objective**—The goal of this study was to examine whether fatty liver and abdominal visceral adipose tissue (VAT) are jointly associated with cardiometabolic abnormalities.

**Methods and Results**—Black participants were from the Jackson Heart Study (n=2882, 65% women) who underwent computed tomography. Fatty liver was measured by liver attenuation in Hounsfield units (LA), and VAT was quantified volumetrically. Cross-sectional associations between LA, VAT, and cardiometabolic risk factors were assessed using linear and logistic regression, and their joint associations were further examined in 4 subgroups: high-LA/low-VAT (n=1704), low-LA/low-VAT (n=422), high-LA/high-VAT (n=436), and low-LA/high-VAT (n=320). Both LA and VAT were associated with most cardiometabolic traits (all  $P < 0.0001$ ), which persisted after additional adjustment for each other (LA,  $P < 0.01$ – $0.0001$ ; VAT,  $P < 0.0001$ ). In bootstrap analyses, the regression coefficient of VAT was significantly greater than LA for triglycerides, high-density lipoprotein cholesterol, impaired glucose, and metabolic syndrome ( $P = 0.009$ – $0.0001$ ). The interaction between LA and VAT was significant for high-density lipoprotein cholesterol ( $P = 0.002$ ), impaired glucose ( $P = 0.003$ ), and metabolic syndrome ( $P = 0.04$ ). Among 4 subgroups, participants with higher VAT and lower LA had higher prevalence of cardiometabolic traits than those with each condition alone.

**Conclusion**—Both fatty liver and VAT are independent correlates of cardiometabolic risk, but the associations are stronger for VAT than for fatty liver. (*Arterioscler Thromb Vasc Biol.* 2011;31:2715-2722.)

**Key Words:** Jackson Heart Study ■ abdominal visceral fat ■ cardiometabolic risk factors ■ fatty liver

Both fatty liver and abdominal visceral adipose tissue (VAT) are important risk factors for the development of cardiometabolic complications due to obesity.<sup>1–4</sup> Epidemiological studies indicate that higher levels of VAT or fatty liver are associated with insulin resistance, metabolic syndrome, dyslipidemia, hypertension, and diabetes.<sup>1,2,5</sup> Moreover, because of the anatomic blood circulation between VAT and the liver, free fatty acids and inflammatory adipokines that are produced by VAT<sup>6,7</sup> can be released into the portal vein and directly transported to the liver, causing fatty liver disease.<sup>3,8,9</sup> These observations have led to a hypothesis that fatty liver may be another important characteristic of fat distribution that is associated with different metabolic risk profiles.<sup>3,8</sup>

Although VAT and the liver are metabolically connected and both are associated with cardiometabolic risk factors,<sup>4,6,9</sup> their joint associations with these risk factors remain unclear.<sup>10</sup> In a cross-sectional study, cardiometabolic abnormalities were associated with increased intrahepatic triglyceride

content but not with high VAT volume, pointing to the possibility that fatty liver, not VAT, is linked to metabolic complications of obesity.<sup>10,11</sup> Other studies, however, have demonstrated that VAT and fatty liver are jointly associated with cardiometabolic abnormalities, suggesting that these 2 fat depots are both important with respect to cardiometabolic abnormalities.<sup>3,4</sup>

Blacks are disproportionately affected by obesity, but the concomitant role of fatty liver and VAT remains unclear.<sup>12–14</sup> Studies have consistently shown that blacks have a lower quantity of VAT and fatty liver,<sup>12,14</sup> despite higher rates of insulin resistance, metabolic syndrome, dyslipidemia, hypertension, and diabetes.<sup>15</sup> This paradox suggests that either the associations of fatty liver or VAT with cardiometabolic risk factors vary across different ethnic groups or higher rates of cardiometabolic disorders in blacks are due to factors above and beyond fatty liver and VAT. Therefore, it remains unclear whether fatty liver is an important correlate of cardiometabolic risk after accounting for VAT or whether

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fatty liver and VAT are jointly associated with cardiometabolic risk in black populations.

Thus, the purpose of the present study is to examine the associations among fatty liver, abdominal VAT, and cardiometabolic abnormalities, and in particular to assess the association of fatty liver with cardiometabolic abnormalities above and beyond abdominal VAT in blacks. This study is part of the Jackson Heart Study (JHS).

## Methods

### Study Sample

The original JHS cohort enrolled participants from September 2000 to March 2004 and comprises 5301 participants between the ages of 21 to 94 years.<sup>16,17</sup> The present study includes a subset of participants (n=2884) who underwent multidetector computed tomography (CT) scanning from 2007 to 2009 as a part of the second JHS Examination (JHS Examination 2).

Overall, 4203 participants attended JHS examination 2 (from 2005–2008). Participants were excluded from the CT scan examination if (1) body weight was greater than 350 lbs ( $\approx$ 160 kg) (n=41); (2) participant was pregnant or had an unknown pregnancy status (n=13); (3) female participants were <40 years of age (n=128); or (4) male participants were <35 years of age (n=48). Of these, 2884 (65% women) underwent multidetector CT assessment for fatty liver. Individuals imaged were further excluded if CT measurements were missing for total abdominal adipose tissue (n=1) or for VAT (n=1), resulting in a final sample size of 2882. The study protocol was approved by the institutional review board of the participating institutions: the University of Mississippi Medical Center, Jackson State University, and Tugaloo College. All participants provided informed consent.

### Multidetector CT Scan Protocol for Measuring Adiposity

The research CT protocol included the heart and lower abdomen using a 16-channel multidetector CT system equipped with cardiac gating (Lightspeed 16 Pro, GE Healthcare, Milwaukee, WI). Quality control and image analysis was performed at a core reading center (Wake Forest University School of Medicine, Winston-Salem, NC). The protocol included scout images, 1 ECG gated series of the entire heart, and a series through the lower abdomen.

The acquired abdominal imaging slices covering the lower abdomen from L3 to S1 were used to quantify VAT. Briefly, 24 contiguous 2-mm thick slices centered on the lumbar disk space at L4 to L5 were used for this analysis; 12 images before the center of the L4 to L5 disk space and 12 images after the disk space were used for quantification of VAT. The abdominal muscular wall was first manually traced, and the fat volumes in different compartments were measured by semiautomatic segmentation technique. Volume analysis software (Advantage Windows, GE Healthcare, Waukesha, WI) was used to segment and characterize each individual voxel as a tissue attenuation of fat using a threshold range of  $-190$  to  $-30$  Hounsfield units. The VAT volumes were the sum of VAT voxels over 24 slices. In this study, the interclass correlation coefficient for interreader comparisons was 0.95 for VAT in a random selected sample of 60 participants.

The CT diagnosis of fatty liver can be made by measuring CT attenuation in Hounsfield units or the difference between the liver and spleen, which have been shown to be inversely correlated with the amount of fat in the liver seen on liver biopsy.<sup>18,19</sup> A more recent study demonstrates that a simple measurement of liver attenuation on unenhanced CT scans is the best method of predicting pathological fat content in the liver.<sup>20</sup> Thus, measurement of liver attenuation in Hounsfield units (LA) was performed on multidetector CT scans of the abdomen at the level of the T12 to L1 intervertebral space and was used to estimate fatty liver (low LA=high fatty liver). The LA was determined by calculating the mean Hounsfield units of 3 regions of interest in the parenchyma of the right lobe of the liver.<sup>19</sup>

One region of interest randomly drawn, avoiding the large vessels and any focal lesions, was considered and each region of interest measured  $100 \pm 13.31$  mm<sup>2</sup>. The correlation coefficient between 2 different readers on a random selected sample of 60 participants was 0.98 for LA, indicating reliable reproducibility of CT imaging measurements.

### Risk Factors and Covariate Assessment

Risk factors and covariates were measured at examination 2 (2005–2008). Body mass index (BMI) was defined as weight (in kilograms) divided by the square of height (in meters). Two measures of the waist (at the level of the umbilicus, in the upright position) were averaged to determine waist circumference for each participant. Fasting blood samples were collected according to standardized procedures, and the assessment of plasma glucose and lipids was performed at the Central Laboratory (University of Minnesota) as previously described.<sup>16,17</sup> Sitting blood pressure was measured twice at 5-minute intervals, and the average of 2 measurements was used for analysis.

Participants were considered to have hypertension if they were taking antihypertensive medications, self-reported a diagnosis of hypertension, or their systolic pressure was  $\geq 140$  mm Hg or diastolic pressure was  $\geq 90$  mm Hg. Impaired fasting glucose was defined as fasting plasma glucose of 100 to 125 mg/dL among those not treated for diabetes. Diabetes was defined as a fasting plasma glucose level  $\geq 126$  mg/dL or treatment with insulin or hypoglycemic agents. High triglycerides level were defined as fasting plasma triglyceride level  $\geq 150$  mg/dL, and low high-density lipoprotein cholesterol (HDL-C) levels were defined as fasting plasma HDL-C level  $< 40$  mg/dL in men and  $< 50$  in women. Participants were considered current smokers if they had smoked, used chewing tobacco or nicotine gum, or were wearing a nicotine patch at the time of interview. Daily alcohol consumption were assessed by the validated food frequency questionnaires,<sup>21</sup> and participants were defined as alcohol drinkers if they drank more than 14 drinks per week (men) or more than 7 drinks per week in women. Obesity was defined by BMI of at least 30 kg/m<sup>2</sup>, and modified National cholesterol Education Program Adult Treatment Panel III criteria were used to define the metabolic syndrome.<sup>22</sup>

To define the individual with hepatic steatosis, a healthy referent sample was created by hierarchical exclusion of the presence of hypertension, triglycerides  $\geq 150$  mg/dL or taking lipid medications, HDL-C  $< 40$  mg/dL in men or  $< 50$  in women, fasting glucose  $\geq 126$  mg/dL or diabetes (n=2551), prevalent cardiovascular disease (n=9), BMI  $< 18.5$  kg/m<sup>2</sup> (n=115), and alcohol drinkers (n=31), resulting in final healthy referent sample size of 178. The lowest 10th percentile was chosen as a cutoff point from this healthy referent sample to define the prevalence of hepatic steatosis.<sup>23</sup>

### Statistical Analysis

LA and triglycerides were normalized by logarithmic transformation. Age-adjusted Pearson correlations of log LA was performed with each of the metabolic risk factors, including VAT, BMI, systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, and HDL-C. VAT and log LA were standardized to a mean of 0 and a standard deviation (SD) of 1. A multivariable regression model was constructed with VAT or log LA as the independent variable and each of metabolic risk factors as the dependent variables. Three models were generated in stages: (1) the multivariable-adjusted model, with covariates including age; gender; smoking and alcohol consumption; and medications for hypertension, diabetes, and dyslipidemia; (2) a second model, in which the first model was additionally adjusted for BMI; and (3) a third model, in which the first model was additionally adjusted for VAT. Interactions between LA and VAT were examined for each of the outcomes after accounting for VAT in the model. To further assess whether VAT or LA was more strongly associated with risk factors, a bootstrap analysis was performed, and the differences in standardized regression coefficients for VAT and LA were compared. Specifically, 5000 samples with replacement were randomly selected from original sample. An overall estimate

**Table 1. Clinical Characteristics (Mean±SD) of Study Participants Who Underwent Computed Tomography Exam by Tertiles of Liver Attenuation (Low Liver Attenuation=High Liver Fat)**

	Tertile 1 (n=961)	Tertile 2 (n=960)	Tertile 3 (n=961)	P for Difference
<b>Covariates</b>				
Age, y	59±10	59±11	59±11	0.82
Women, %	60	64	71	0.0001
Smoking status, %	7.4	6.8	6.0	0.49
Alcohol drinker	40.9	28.8	30.3	0.06
<b>Fat-related</b>				
LA (HU)	49.4±8.6	60.5±1.7	67.3±3.4	0.0001
Abdominal VAT, cm <sup>3</sup>	971.1±404.0	790.6±363.7	730.1±338.8	0.0001
Abdominal SAT, cm <sup>3</sup>	2489.2±1051	2268.3±985	2232.7±987.8	0.0001
BMI, kg/m <sup>2</sup>	33.2±6.7	31.2±6.1	30.5±6.2	0.0001
WC, cm	105.9±15.2	100.6±14.4	100.3±80.0	0.014
Obesity, %	65.1	53.8	46.0	0.0001
Hepatic steatosis, %	84.5	0	0	0.0001
<b>BP-related</b>				
Systolic BP, mm Hg	127±17	127±18	127±34	0.92
Diastolic BP, mm Hg	77±10	77±10	77±10	0.30
Hypertension, %	76.6	71.8	69.3	0.002
<b>Glucose-related</b>				
Fasting glucose, mg/dL	111.7±39.6	101.7±31.4	103.3±30.1	0.0001
HbA1C, %	6.3±1.2	6.0±1.0	5.9±0.9	0.0001
Impaired glucose, %	20.0	17.6	16.1	0.08
Diabetes mellitus, %	35.5	22.0	19.7	0.0001
<b>Lipid-related</b>				
TRG, mg/dL*	99 (70, 146)	84 (61, 117)	81 (60, 117)	0.0001
High TRG, %	19.0	9.6	10.6	0.0001
HDL-C, mg/dL	51.3±15.0	55.7±15.5	56.5±0.5	0.0001
Low HDL, %	48.8	37.7	39.7	0.0001
Syndrome-related metabolic syndrome, %	69.1	55.5	51.8	0.0001

LA indicates liver attenuation; HU, Hounsfield units; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; BP, blood pressure; HbA1C, hemoglobin A1C; TRG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HDL, high-density lipoprotein.

\*Presented as median (25th, 75th percentiles).

of the VAT and LA regression coefficients, their variance, and their covariance were obtained from 2 multivariable linear regressions (1 with VAT and another with log LA) on the 5000 samples. A  $z$ -statistic was used to test the absolute difference in regression coefficients between VAT and LA.<sup>24</sup>

In addition, secondary analyses were conducted to examine the joint associations of LA and VAT with metabolic parameters. Study participants were stratified into 4 groups based on the 75th percentile of VAT and the 25th percentile of LA, in which the highest risk categories had VAT in the 75th percentile and LA in the 25th percentile (low LA=high fatty liver).<sup>19</sup> Therefore, 4 groups (high-LA/low-VAT, low-LA/low-VAT, high-LA/high-VAT, and low-LA/high-VAT) were derived. A multivariable logistic regression model was used to assess these phenotypes in association with cardiometabolic risk factors as compared with a reference group (high-LA/low-VAT).

All computations were performed by SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

## Results

### Study Sample Characteristics by Tertiles of LA

Overall, 2882 participants (65% women) with an average age of 60 years were available for analysis. In the lowest LA tertile, cardiometabolic risk factor prevalence was generally higher, compared with the highest LA tertile (Table 1). Approximately 55% were obese, 59% had metabolic syndrome, and 27.8% had hepatic steatosis.

### Correlations With Liver Attenuation

Age-adjusted correlations of log LA with metabolic risk factors are displayed in Table 2. Log LA was inversely associated with all cardiometabolic risk factors tested, including VAT, BMI, waist circumference, triglycerides, fasting plasma glucose, and hemoglobin A1C, and positively associated with HDL-C.

**Table 2. Age-Adjusted Pearson Correlation Coefficients Between Log LA and Metabolic Risk Factors**

	Log LA	P	VAT	P
Log LA			-0.30	0.0001
VAT	-0.30	0.0001		
SAT	-0.09	0.0001	0.35	0.0001
BMI	-0.19	0.0001	0.55	0.0001
WC	-0.04	0.05	0.23	0.0001
Systolic BP	-0.01	0.52	0.04	0.10
Diastolic BP	-0.01	0.45	0.06	0.01
Log TRG	-0.22	0.0001	0.32	0.0001
HDL-C	0.16	0.0001	-0.34	0.0001
Fasting glucose	-0.16	0.0001	0.23	0.0001
HbA1C	-0.20	0.0001	0.27	0.0001

LA indicates liver attenuation in Hounsfield units; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; BP, blood pressure; TRG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HbA1C, hemoglobin A1C.

### Multivariable-Adjusted Regression Model With LA and Metabolic Risk Factors

The results of the multivariable-adjusted regressions for the association of log LA are summarized with continuous variables in Table 3 and dichotomous metabolic risk factors in Table 4. We observed strong and consistent associations between log LA and most cardiometabolic outcomes. For example, lower log LA (per 1-SD decrement) was associated

with higher fasting plasma glucose levels ( $3.79 \pm 0.7$  mg/dL,  $P < 0.0001$ ) after multivariable adjustment. The association persisted after additional adjustment for BMI ( $P = 0.0001$ ) and VAT ( $P = 0.004$ ). When comparing the association with cardiometabolic outcomes between VAT and log LA using bootstrap with 5000 replications, the regression coefficients were stronger for VAT with triglycerides (VAT  $0.18 \pm 0.1$  versus log LA  $-0.12 \pm 0.0$ ;  $P < 0.0008$  for difference) and HDL-C (VAT  $-4.74 \pm 0.3$  versus log LA  $2.00 \pm 0.3$ ;  $P < 0.0001$ ) than for log LA (Table 3).

For dichotomous variables, significant associations with log LA were also observed for impaired glucose, high triglycerides, low HDL-C, hypertension, diabetes, and the metabolic syndrome (Table 4). These associations persisted after additional adjustment for BMI or for VAT, with the exception of hypertension and impaired glucose. For differences in the regression coefficients between log LA and VAT with all risk factors examined, the magnitude of the associations was consistently stronger for VAT than for log LA with impaired glucose, high triglyceride, low HDL-C, and metabolic syndrome ( $P = 0.009-0.0001$ ) (Tables 3 and 4).

We also observed significant interactions between log LA and VAT for HDL-C ( $P = 0.009$ ), impaired fasting glucose ( $P = 0.003$ ), and metabolic syndrome ( $P = 0.04$ ) (Tables 3 and 4), suggesting that participants with higher VAT and lower log LA had lower HDL-C levels, more impaired fasting glucose, and more metabolic syndrome compared with those with each condition alone.

**Table 3. A Multivariable-Adjusted\* Regression Coefficient of Continuous Variables for VAT and Log LA (per 1 SD Increment) With Cardiometabolic Risk Factors**

	MV* Regression Coefficients	P for Significance	P for Difference Between VAT and LA	MV* Regression Coefficients After BMI Adjustments	P for Significance	MV* Regression Coefficients After VAT or LA Adjustments	P for Significance	P for VAT and LA Interaction
<b>SBP</b>								
Log LA	$-0.47 \pm 0.3$	0.17	0.79	$-0.34 \pm 0.3$	0.32	$-0.21 \pm 0.4$	0.38	0.14
VAT	$0.59 \pm 0.4$	0.09		$0.46 \pm 0.4$	0.28	$0.30 \pm 0.4$	0.17	
<b>DBP</b>								
Log LA	$-0.31 \pm 0.2$	0.11	0.84	$-0.28 \pm 0.2$	0.15	$-0.23 \pm 0.2$	0.26	0.82
VAT	$0.34 \pm 0.2$	0.10		$0.39 \pm 0.2$	0.10	$0.27 \pm 0.2$	0.20	
<b>FPG</b>								
Log LA	$-3.79 \pm 0.7$	0.0001	0.37	$-3.21 \pm 0.8$	0.0001	$-2.70 \pm 0.8$	0.0004	0.22
VAT	$4.62 \pm 0.7$	0.0001		$4.86 \pm 0.9$	0.0001	$3.84 \pm 0.8$	0.0001	
<b>HbA1C</b>								
Log LA	$-0.15 \pm 0.0$	0.0001	0.22	$-0.13 \pm 0.0$	0.0001	$-0.11 \pm 0.0$	0.0001	0.36
VAT	$0.18 \pm 0.0$	0.0001		$0.16 \pm 0.0$	0.0001	$0.15 \pm 0.0$	0.0001	
<b>Log TRG</b>								
Log LA	$-0.12 \pm 0.0$	0.0001	0.0008	$-0.11 \pm 0.0$	0.0001	$-0.07 \pm 0.0$	0.0001	0.11
VAT	$0.18 \pm 0.1$	0.0001		$0.20 \pm 0.1$	0.0001	$0.15 \pm 0.1$	0.0001	
<b>HDL-C</b>								
Log LA	$2.00 \pm 0.3$	0.0001	0.0001	$1.39 \pm 0.3$	0.0001	$0.76 \pm 0.3$	0.01	0.002
VAT	$-4.74 \pm 0.3$	0.0001		$-3.65 \pm 0.4$	0.0001	$-4.51 \pm 0.3$	0.0001	

MV indicates multivariable; VAT, visceral adipose tissue; LA, liver attenuation in Hounsfield units; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; TRG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

\*Adjusted for age, gender, smoking, alcohol, and medications for hypertension, diabetes mellitus, or dyslipidemia.



**Table 4. A Multivariable-Adjusted\* Odds Ratio of Dichotomous Variables for VAT and Log LA (per 1 SD Increment) With Cardiometabolic Risk Factors**

	MV* Regression Coefficients	P for Significance	P for Difference Between VAT and LA	MV* Regression Coefficients After BMI Adjustments	P for Significance	MV* Regression Coefficients After VAT or LA Adjustments	P for Significance	P for VAT and LA Interaction
<b>HTN</b>								
Log LA	0.84 (0.7–0.9)	0.04	0.85	0.87 (0.7–1.1)	0.11	0.89 (0.7–1.1)	0.14	0.24
VAT	1.21 (1.0–1.4)	0.03		1.17 (0.9–1.4)	0.13	1.14 (0.9–1.4)	0.10	
<b>Impaired G</b>								
Log LA	0.85 (0.7–0.8)	0.0009	0.009	0.88 (0.7–0.9)	0.01	0.94 (0.8–1.0)	0.21	0.003
VAT	1.46 (1.3–1.6)	0.0001		1.39 (1.2–1.6)	0.0001	1.36 (1.2–1.6)	0.0001	
<b>DM</b>								
Log LA	0.70 (0.6–0.8)	0.0001	0.79	0.76 (0.6–0.9)	0.001	0.75 (0.6–0.9)	0.001	0.64
VAT	1.45 (1.2–1.7)	0.0001		1.18 (0.9–1.5)	0.17	1.10 (0.8–1.4)	0.48	
<b>High TRG</b>								
Log LA	0.72 (0.6–0.8)	0.0001	0.0004	0.74 (0.6–0.8)	0.0001	0.81 (0.7–0.9)	0.0001	0.66
VAT	1.73 (1.6–1.9)	0.0001		1.84 (1.6–1.9)	0.0001	1.62 (1.4–1.8)	0.0001	
<b>Low HDL</b>								
Log LA	0.81 (0.7–0.9)	0.0001	0.0003	0.84 (0.7–0.9)	0.0001	0.89 (0.8–0.9)	0.008	0.56
VAT	1.51 (1.4–1.6)	0.0001		1.43 (1.3–1.6)	0.0001	1.45 (1.3–1.6)	0.0001	
<b>MetS</b>								
Log LA	0.64 (0.6–0.7)	0.0001	0.0001	0.74 (0.6–0.8)	0.0001	0.82 (0.7–0.9)	0.004	0.04
VAT	3.32 (2.9–3.9)	0.0001		2.54 (2.1–3.0)	0.0001	3.16 (2.7–3.7)	0.0001	

VAT, visceral adipose tissue; LA, liver attenuation in Hounsfield units; HTN, hypertension; DM, diabetes mellitus; TRG, triglyceride; HDL, high-density lipoprotein; MetS, metabolic syndrome.

\*Adjusted for age; gender; smoking; alcohol; and medications for HTN, DM, or dyslipidemia.

### Multivariable-Adjusted Association of Four Stratified Log LA/VAT Patterns and Cardiometabolic Risk Factors

We assessed the joint association of log LA and VAT with cardiometabolic risk factors. When the study sample was derived into 4 groups based on 25th percentile of log LA and 75th percentile of VAT in secondary analyses, significant differences were observed for all risk factors examined among 4 groups, except for blood pressure and hypertension (all  $P < 0.0001$ ; Table 5).

Among continuous variables, higher levels of fasting glucose, hemoglobin A1C, and triglycerides and lower levels of HDL-C were observed in the low-LA/high-VAT group, the low-LA/low-VAT group, and the high-LA/high-VAT group after adjustment for age, gender, smoking, alcohol consumption, BMI, and medications for hypertension, diabetes, and dyslipidemia as compared with the high-LA/low-VAT group ( $P = 0.002$ – $0.0001$ ). Similar patterns were also observed for dichotomous variables. The risk factor prevalence was higher with greater levels of VAT (high-LA/high-VAT;  $P < 0.0001$ ), lower levels of log LA (low-LA/low-VAT;  $P = 0.001$ – $0.0001$ ) or both (low-LA/high-VAT;  $P < 0.0001$ ) as compared with a reference group (high-LA/low-VAT) (Figure).

## Discussion

### Principal Findings

Both low LA (ie, high level of fatty liver) and VAT are independently associated with cardiometabolic risk factors,

including fasting glucose, hemoglobin A1C, triglycerides, HDL-C, diabetes, and metabolic syndrome. The significant associations persisted after additional adjustment for each other. However, the magnitude of the effect of VAT was larger than that of LA in the association with cardiometabolic risk factors, with the exception of blood pressure, fasting glucose, and hemoglobin A1C.

### In the Context of the Current Literature

Studies have consistently documented the association of fatty liver with VAT and its predominant role in the regulation of glucose and lipid metabolism.<sup>3,8,9,13</sup> Elevated fatty liver has been found to be associated with cardiometabolic risk factors independent of VAT.<sup>3,10,25,26</sup> Thus, several studies suggest that commonly observed associations of cardiometabolic abnormalities with VAT is primarily due to elevated fatty liver associated with obesity.<sup>10,25,26</sup> Indeed, fatty liver has been shown in our study to be significantly associated with cardiometabolic risk factors independent of VAT. However, our study also found that the associations with triglycerides and HDL-C were stronger for VAT as compared with fatty liver, suggesting that VAT may be more important for metabolic abnormalities than fatty liver. This is in contrast to the finding from the prior literature in which insulin action was impaired and hepatic very-low-density lipoprotein-triglyceride secretion rate was increased in subjects with high liver fat content but matched on VAT volume as compared with subjects with high VAT but matched on liver fat content, demonstrating that fatty liver, not VAT, is linked with

**Table 5. Multivariable-Adjusted\* Means±SD of Continuous Variables or Odds Ratio of Dichotomous Variables for Four VAT/LA Patterns**

	High-LA/ Low-VAT (n=1704)	Low-LA/ Low-VAT (n=422)	High-LA/ High-VAT (n=436)	Low-LA/ High-VAT (n=320)	P for Difference
Continuous variables					
Age	59±11	57±10	63±10	61±9	0.0001
VAT	630.6±216	739.0±205	1307.0±281	1373.7±291	0.0001
LA (HU)	63.2±4.8	48.6±7.8	62.4±4.5	45.1±9.4	0.0001
BMI	29.9±5.6	31.9±6.1	35.2±6.5	36.2±6.8	0.0001
SBP	126±19	126±17	128±18	129±17	0.89
DBP	77±10	77±11	77±11	77±10	0.67
FPG	100.4±28	109.8±34	113.7±41	118.5±46	0.0001
HbA1C	5.86±1.0	6.25±1.1	6.31±1.1	6.61±1.4	0.0001
Log TRG	4.4±0.5	4.6±0.9	4.7±0.9	4.8±1.8	0.0001
HDL	57.2±15	51.9±15	50.5±13	48.1±13	0.0001
Dichotomous variables					
Women, %	68	64	59	57	0.0001
HTN†	Referent	1.35 (0.9–2.1)	1.30 (0.8–2.2)	1.41 (0.8–2.5)	0.38
DM†	Referent	1.89 (1.1–3.2)	0.92 (0.5–1.8)	2.21 (1.2–4.0)	0.008
Impaired Glu†	Referent	1.77 (1.3–2.3)	1.80 (1.3–2.4)	1.42 (0.9–2.0)	0.0001
High TRG†	Referent	2.42 (1.7–3.4)	2.92 (2.0–4.1)	4.36 (3.0–6.3)	0.0001
Low HDL†	Referent	1.37 (1.1–1.7)	1.35 (1.1–1.7)	2.11 (1.6–2.8)	0.0001
MetS†	Referent	1.55 (1.1–2.1)	2.56 (1.8–3.7)	3.02 (1.9–4.7)	0.0001

VAT, visceral adipose tissue; LA, liver attenuation; HU, Hounsfield units; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; TRG, triglyceride; HDL, high-density lipoprotein; HTN, hypertension; DM, diabetes mellitus; Glu, glucose; MetS, metabolic syndrome.

\*Multivariable-adjusted for age; gender; BMI; smoking; alcohol; and medications for hypertension, diabetes, and dyslipidemia.

†Presented as median (25th, 75th percentiles).

metabolic complications of obesity.<sup>10</sup> The discrepancy between the 2 studies may be due to the matching scheme in their study design, which results in a nongeneralizable and obscure subset of the entire data set, or to the black samples in our study.

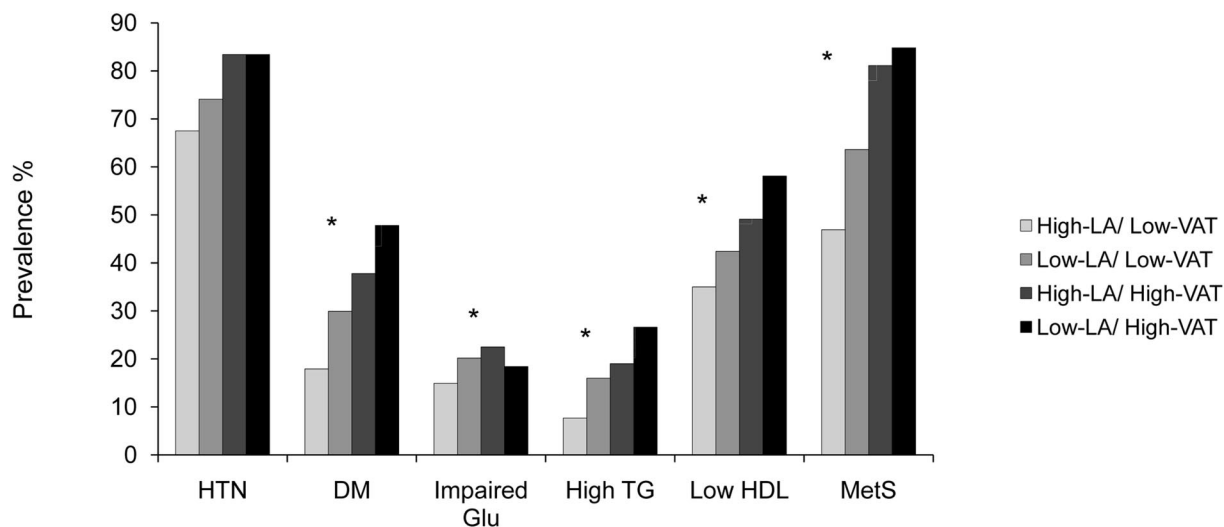
The finding that blacks have lower levels of abdominal VAT and fatty liver<sup>6,12,14,27</sup> yet experience higher levels of cardiometabolic risk compared with other ethnic groups<sup>15</sup> remains a paradox. However, the associations of cardiometabolic risk factors with fatty liver and abdominal VAT in blacks are not fully explored. Results from our current study demonstrate that both fatty liver and VAT are independent risk factors for cardiometabolic abnormalities, which is consistent with prior studies.<sup>3,8,9</sup> More importantly, this association with cardiometabolic abnormalities in our study is stronger for VAT than for fatty liver. These observations not only support a consistent and particular role for fatty liver and VAT in association with cardiometabolic risk factors but also reinforce the importance of abdominal VAT in pathogenesis of lipid-related metabolic risk in black populations.

### Potential Mechanisms

It has been hypothesized that the adverse effects of fatty liver are related to metabolic connection with VAT.<sup>8,9</sup> However, it is uncertain whether a relationship between VAT and fatty

liver plays a joint role in the development of cardiometabolic abnormalities. In fact, only ≈20% of total nonesterified fatty acid derived from lipolysis of VAT are delivered into the liver in obese individuals.<sup>28</sup> Even though VAT is the strongest correlate of fatty liver, the correlations reported in the present study (−0.30) and in the Framingham Heart Study (−0.34) are relatively modest.<sup>3</sup> These observations suggest that although VAT and fatty liver are metabolically connected, this connection may not be mediated via fatty acid delivery and uptake alone.

Different pathways, including patterns of proteins and adipokines associated with cardiometabolic abnormalities, could explain the differential influence of VAT and fatty liver on metabolic profiles. For example, C-reactive protein, leptin, interleukin-6, and adiponectin are associated with visceral adiposity and are closely associated with cardiometabolic abnormalities,<sup>7,29</sup> whereas  $\alpha_2$ -Heremans-Schmid glycoprotein/fetuin-A and circulating retinol-binding protein 4 are produced in the liver and are highly associated with insulin resistance and fat accumulation in the liver.<sup>30,31</sup> Indeed, participants with high VAT and high fatty liver in our study have high rates of adverse cardiometabolic phenotypes, particularly compared with those with high VAT or high fatty liver alone. Our results support that VAT and fatty liver differentially but interactively associate with cardiometabolic abnormalities.



\* represent probability ( $p < 0.0001$ ) for linear trend across four groups.

VAT: visceral adipose tissue; LA: liver attenuation in Hounsfield Units; Glu: glucose; TG: triglyceride; HDL: high-density lipoprotein.

**Figure.** Prevalence of hypertension (HTN), diabetes mellitus (DM), impaired fasting glucose (Glu), high triglyceride (TG), low HDL cholesterol, and metabolic syndrome (MetS) among 4 group patterns (high-LA/low-VAT,  $n=1704$ ; low-LA/low-VAT,  $n=422$ ; high-LA/high-VAT,  $n=436$ ; low-LA/high-VAT,  $n=320$ ). \* $P < 0.0001$  for linear trend across 4 groups. VAT indicates visceral adipose tissue; LA, liver attenuation in Hounsfield units.

## Implications

The epidemic of obesity is particularly pronounced in blacks. Paradoxically, blacks also have lower levels of fatty liver and abdominal fat. The results of the present study demonstrate that both fatty liver and abdominal fat are independently associated with cardiometabolic abnormalities, but the association is stronger for VAT than for fatty liver. Whether attempts to reduce VAT and liver fat in blacks can help lower cardiovascular outcomes requires further study.

## Strengths and Limitations

The strength of the present study is the large, well-characterized black cohort with a wealth of metabolic traits and covariates measured. Some limitations warrant mention. The findings are cross-sectional and derived from an observational study; thus, neither temporality nor causality can be inferred. The study cannot directly take insulin resistance and physical activity into account because these 2 variables were not measured at the contemporaneous JHS examination. CT is a relatively insensitive measure of fatty liver compared with hepatic triglyceride content measured by proton magnetic resonance spectroscopy,<sup>4,12</sup> which may bias our results toward the null and underestimate the relative strength of the association between fatty liver and risk factors.

## Conclusions

Both fatty liver and VAT are independently associated with cardiometabolic abnormalities, but the associations with triglyceride and HDL-C are stronger for VAT than for fatty liver.

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## Disclosures

None.

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