

## Associations of Obesity With Lipoprotein Subfractions in Japanese American, African American, and Korean Men

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### ABSTRACT

**Background:** Both indices of obesity and lipoprotein subfractions contribute to coronary heart disease risk. However, associations between indices of obesity and lipoprotein subfractions remain undetermined across different ethnic groups.

**Objective:** This study aims to examine the associations of indices of obesity in Japanese Americans, African Americans, and Koreans with lipoprotein subfractions.

**Methods:** A population-based sample of 230 Japanese American, 91 African American, and 291 Korean men ages 40 to 49 was examined for indices of obesity—that is, visceral and subcutaneous adipose tissue (VAT and SAT, respectively); waist circumference; and body mass index—and for lipoprotein subfractions by nuclear magnetic resonance spectroscopy. Multiple regression analyses were performed in each of the 3 ethnic groups to examine the associations of each index of obesity with lipoprotein.

**Conclusions:** VAT had significant positive associations with total and small low-density lipoprotein (LDL) and a significant negative association with large high-density lipoprotein (HDL) in all 3 ethnicities ( $p < 0.01$ ). SAT, waist circumference, and body mass index had significant positive associations with total and small LDL in only Japanese Americans and Koreans, whereas these indices had significant inverse associations with large HDL in all ethnic groups ( $p < 0.01$ ). Compared with SAT, VAT had larger  $R^2$  values in the associations with total and small LDL and large HDL in all 3 ethnic groups. VAT is significantly associated with total and small LDL and large HDL in all 3 ethnic groups. The associations of SAT, waist circumference, and body mass index with lipoprotein subfractions are weaker than the associations of VAT in all 3 ethnic groups.

Coronary heart disease (CHD) is the leading cause of death in the United States [1] and worldwide [2]. Thus, preventing CHD is of great interest from both a clinical and a public health perspective. Current clinical practice guidelines, such as those by the National Cholesterol Education Program Adult Treatment Panel, recommend measuring standard lipids to assess CHD risk and stratify risk categories [3]. Our ability to estimate the risk of developing CHD is limited, however, and intense efforts have been made to determine whether additional examination would improve the accuracy of CHD risk estimation [4,5]. Such efforts include measuring lipoprotein subfractions.

Lipoprotein subfractions can be quantified by nuclear magnetic resonance spectroscopy [6,7]. Some subfractions are reported to be associated with CHD. Total low-density lipoprotein (LDL) number and small LDL particles, for

example, are strong predictors of CHD. Small high-density lipoprotein (HDL) is positively associated with CHD, whereas large HDL is inversely associated [8,9].

Many epidemiological studies have demonstrated strong associations of indices of obesity, such as visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), waist circumference (WC), and body mass index (BMI), with CHD and its risk factors [10–12]. Evidence suggests body fat distribution, such as VAT, is more strongly associated with CHD than BMI or WC are [11,13].

Recently, several studies have examined the associations between indices of obesity and lipoprotein subfractions. In these studies, VAT is more strongly associated with risk factors and lipoprotein subfractions than SAT is [11,14]. We have reported that VAT and SAT are associated with higher particle concentrations of total, large, and medium very low-density lipoprotein (VLDL), small LDL,

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and large HDL in a population-based sample of U.S. white and Japanese middle-aged men [15]. Our study also indicates the associations of VAT with lipoprotein subfractions are stronger than those for SAT. However, few studies have investigated associations between indices of obesity (i.e., VAT, SAT, WC, and BMI) and lipoprotein subfractions among different ethnicity groups from a community-based population. This study examined the association between indices of obesity and lipoprotein subfractions for Japanese Americans (JA), African Americans (AA), and Koreans from a community-based sample.

## METHODS

### Study participants

During 2002 to 2006, 712 men ages 40 to 49 were randomly selected: 303 JA men from a representative sample of offspring to fathers who participated in the Honolulu Heart Program, Honolulu, Hawaii, USA [16]; 107 AA men from Allegheny County, Pennsylvania, USA [17]; and 302 Korean men from Ansan, Gyeonggi-do, South Korea. JA men were the third or fourth generation of JA without ethnic admixture. All the participants were without clinical cardiovascular disease or other severe diseases [17]. Men in Honolulu were randomly selected from the offspring of the members of the Honolulu Heart Program [18]. Men in Allegheny County, Pennsylvania, USA, were randomly selected from the voter registration list. The voter registration list is very complete. Men in South Korea were randomly selected from the Korean Health and Genome Study, an ongoing population-based prospective cohort study [19]. The rate of participation was about 50% at each site. This rate of participation is much higher than for the MESA (Multi-Ethnic Study of Atherosclerosis) [20] and is comparable with the CARDIA (Coronary Artery Risk Development in Young Adults) [21] and the CHS (Cardiovascular Health Study) [22].

Of the original sample, we excluded men taking lipid-lowering medications ( $n = 83$ ) and individuals with missing values ( $n = 17$ ). The final sample was 612 subjects (230 JA, 91 AA, and 291 Koreans). Written informed consent was obtained from each participant. The study was approved by the institutional review boards of the following institutions: the Kuakini Medical Center, Honolulu, Hawaii, USA; the University of Pittsburgh, Pittsburgh, Pennsylvania, USA; and Korea University, Seoul, South Korea.

All participants underwent a physical examination and laboratory assessment and completed a lifestyle questionnaire (e.g., smoking and alcohol consumption), as described previously [17]. Venipuncture was performed after a 12-h fast, early in the morning of the clinic visit. Samples were stored at  $-80^{\circ}\text{C}$  and shipped on dry ice to the University of Pittsburgh to determine lipids, glucose, and other factors. Serum lipids were determined using standardized methods by the Centers for Disease Control and Prevention. Intra-assay coefficients of variation for total cholesterol, triglycerides, and HDL-C were 1.8%, 1.8%,

and 3.5%, respectively. Serum glucose was determined by an enzymatic assay. An intra-assay coefficient of variation for glucose was 1.8%. Data collection was standardized across the research centers.

### Body mass index and abdominal adiposity indices

BMI was calculated using body weight and height ( $\text{kg}/\text{m}^2$ ). WC was measured twice at the umbilical level using a measuring tape while the participant was standing upright in underwear. An average of the 2 measurements was used. VAT and SAT were determined as previously described [23]. Briefly, VAT and SAT areas were measured at the level between the fourth and fifth lumbar vertebrae using computed tomography images obtained with the same apparatus at each site (GE-Imatron C150; GE Medical System, South San Francisco, California, USA). All computed tomography images were read at the Cardiovascular Institute, University of Pittsburgh, using image analysis software by 1 trained reader (AccuImage; Accu-Image Diagnostic Corporation, San Francisco, California, USA).

### Lipoprotein measurement

Nuclear magnetic resonance spectroscopy (LipoScience, Inc., Raleigh, North Carolina, USA) was performed to quantify serum lipoproteins of different sizes [24]. Particle concentrations of the following lipoproteins were determined: VLDL (large:  $>60$  nm; medium: 35–60 nm; small: 27–35 nm); LDL (intermediate-density lipoprotein: 23–27 nm; large: 21.3–23 nm; small: 18.3–21.2 nm); and HDL (large: 8.8–13.0 nm; medium: 8.2–8.8 nm; small: 7.3–8.2 nm) [8]. Weighted average particle sizes were calculated from the subclass levels.

### Statistical analyses

Values of lipoprotein subfractions were positively skewed and log-transformed to approximate the normality. To examine the correlations among obesity indices, we used the Spearman rank correlation. To examine the association of each obesity index—BMI, WC, SAT, and VAT (a primary predictor variable)—with each lipoprotein (an outcome variable), multiple linear regression analyses were performed. In the regression model, values of lipoprotein were log-transformed to approximate the normality, and age, pack-year smoking, and amount of alcohol consumption per day were adjusted. Statistical significance level was considered to be 0.01. All statistical analyses were performed with IBM SPSS Statistics (version 20, IBM, Armonk, New York, USA).

## RESULTS

The baseline characteristics of study subjects are presented in Table 1. Mean BMI ( $\text{kg}/\text{m}^2$ ) differed significantly among the 3 groups: 27.3 for JA; 29.6 for AA; and 24.7 for Koreans. JA had significantly higher VAT and serum

**TABLE 1.** Basic characteristics of the study participants during 2002 to 2006 (N = 612)

	Japanese Americans	African Americans	Koreans	p Value
n	230	91	291	
Age, yrs	46.0 ± 2.9 (45.7, 46.4)	44.7 ± 2.8 (44.1, 45.2)	44.8 ± 2.8 (44.4, 45.1)	<0.001* <sup>†</sup>
BMI, kg/m <sup>2</sup>	27.3 ± 4.0 (26.8, 27.8)	29.6 ± 5.9 (28.4, 30.8)	24.7 ± 2.7 (24.4, 25.0)	<0.001* <sup>†‡</sup>
WC, cm	92.2 ± 10.2 (90.8, 93.4)	98.9 ± 13.4 (96.1, 101.6)	83.4 ± 7.1 (82.6, 84.2)	<0.001* <sup>†‡</sup>
VAT, cm <sup>2</sup>	97.5 ± 39.0 (92.3, 102.5)	79.7 ± 36.7 (72.1, 87.4)	77.9 ± 28.5 (74.6, 81.2)	<0.001* <sup>†</sup>
SAT, cm <sup>2</sup>	131.0 ± 56.6 (123.4, 138.2)	168.1 ± 91.2 (149.1, 187.1)	82.8 ± 31.6 (79.1, 86.4)	<0.001* <sup>†‡</sup>
Systolic BP, mm Hg	126.5 ± 12.1 (124.9, 128.0)	127.1 ± 16.5 (123.6, 130.5)	121.8 ± 14.1 (120.1, 123.4)	<0.001* <sup>‡</sup>
Diastolic BP, mm Hg	76.8 ± 8.7 (75.7, 78.0)	75.4 ± 12.5 (72.8, 78.0)	76.3 ± 11.1 (75.0, 77.6)	NS
Type 2 DM	7.4 (17)	8.8 (8)	9.6 (28)	NS
Smoking, pack-years	4.5 ± 9.3 (3.3, 5.8)	4.8 ± 7.6 (3.3, 6.4)	14.1 ± 14.1 (12.5, 15.8)	<0.001* <sup>‡</sup>
Alcohol, g/day	16.6 ± 28.3 (12.9, 20.3)	14.0 ± 22.8 (9.3, 18.8)	21.7 ± 32.6 (17.9, 25.4)	<0.05 <sup>‡</sup>
Total cholesterol, mmol/l	5.49 ± 0.93 (5.36, 5.59)	5.35 ± 1.20 (5.10, 5.60)	4.99 ± 0.87 (4.90, 5.10)	<0.001* <sup>‡</sup>
Triglycerides, mmol/l	1.99 ± 1.44 (1.80, 2.17)	1.52 ± 0.85 (1.34, 1.69)	1.83 ± 1.19 (1.69, 1.97)	<0.01 <sup>†</sup>
LDL-C, mmol/l	3.31 ± 0.84 (3.20, 3.40)	3.33 ± 1.08 (3.10, 3.56)	2.99 ± 0.81 (2.90, 3.09)	<0.001* <sup>‡</sup>
HDL-C, mmol/l	1.31 ± 0.32 (1.27, 1.35)	1.32 ± 0.41 (1.24, 1.41)	1.19 ± 0.30 (1.15, 1.22)	<0.001* <sup>‡</sup>
Lipoprotein subfractions, log-transformed				
VLDL particle				
Total, nmol/l	1.99 ± 0.22 (1.96, 2.02)	1.81 ± 0.29 (1.75, 1.87)	1.82 ± 0.26 (1.79, 1.85)	<0.001* <sup>†</sup>
Large, nmol/l	0.57 ± 0.43 (0.52, 0.63)	0.49 ± 0.33 (0.42, 0.56)	0.37 ± 0.42 (0.33, 0.43)	0.001* <sup>†‡</sup>
Medium, nmol/l	1.60 ± 0.37 (1.55, 1.65)	1.29 ± 0.49 (1.20, 1.40)	1.27 ± 0.57 (1.22, 1.35)	<0.001* <sup>†</sup>
Small, nmol/l	1.66 ± 0.25 (1.62, 1.69)	1.59 ± 0.25 (1.53, 1.64)	1.53 ± 0.30 (1.50, 1.57)	<0.001* <sup>†</sup>
Average size, nm	1.69 ± 0.06 (1.69, 1.70)	1.71 ± 0.06 (1.70, 1.72)	1.66 ± 0.08 (1.65, 1.67)	<0.001* <sup>‡</sup>
LDL particle				
Total, nmol/l	3.13 ± 0.14 (3.10, 3.14)	3.15 ± 0.14 (3.11, 3.17)	3.05 ± 0.14 (3.03, 3.06)	<0.001* <sup>‡</sup>
IDL, nmol/l	1.53 ± 0.70 (1.45, 1.63)	1.64 ± 0.54 (1.52, 1.75)	0.99 ± 0.73 (0.91, 1.08)	<0.001* <sup>‡</sup>
Large, nmol/l	2.38 ± 0.46 (2.31, 2.43)	2.60 ± 0.33 (2.52, 2.67)	2.59 ± 0.28 (2.56, 2.62)	<0.001* <sup>†</sup>
Small, nmol/l	2.87 ± 0.51 (2.80, 2.93)	2.86 ± 0.42 (2.76, 2.94)	2.64 ± 0.61 (2.58, 2.72)	<0.001* <sup>‡</sup>
Average size, nm	1.33 ± 0.02 (1.33, 1.34)	1.34 ± 0.02 (1.33, 1.34)	1.34 ± 0.02 (1.34, 1.34)	<0.001* <sup>†</sup>
HDL particle				
Total, nmol/l	1.56 ± 0.12 (1.56, 1.57)	1.50 ± 0.09 (1.48, 1.52)	1.46 ± 0.08 (1.45, 1.47)	<0.001* <sup>†‡</sup>
Large, nmol/l	0.79 ± 0.23 (0.77, 0.83)	0.76 ± 0.25 (0.71, 0.81)	0.71 ± 0.22 (0.69, 0.74)	<0.001* <sup>†</sup>
Medium, nmol/l	0.45 ± 0.35 (0.41, 0.50)	0.22 ± 0.27 (0.17, 0.28)	0.15 ± 0.25 (0.12, 0.18)	<0.001* <sup>†</sup>
Small, nmol/l	1.44 ± 0.12 (1.43, 1.45)	1.40 ± 0.10 (1.38, 1.42)	1.36 ± 0.10 (1.35, 1.38)	<0.001* <sup>†‡</sup>
Average size, nm	0.99 ± 0.02 (0.99, 0.99)	0.99 ± 0.02 (0.98, 0.99)	0.99 ± 0.02 (0.99, 0.99)	NS

Values are means ± SD for continuous variables and percentages for categorical variables. The p values for continuous variables were obtained from analysis of variance and for categorical variables were from chi-square test. The 95% confidence intervals are shown in parentheses for continuous variables. BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VLDL, very low-density lipoprotein; WC, waist circumference.

\*Significant between Japanese Americans and Koreans.

<sup>†</sup>Significant between Japanese Americans and African Americans.

<sup>‡</sup>Significant between Koreans and African Americans.

triglyceride levels. AA had significantly higher BMI and SAT. AA also had significantly lower serum triglyceride levels. Koreans had significantly lower BMI, WC, and SAT. Koreans also had significantly lower serum total cholesterol, LDL cholesterol, and HDL cholesterol levels. Average concentrations or sizes of all the lipoprotein subfractions, except for HDL cholesterol size, were significantly different among the 3 groups (Table 1).

### Correlations among VAT, SAT, WC, and BMI

Correlations among indices of obesity within the 3 groups are shown in Table 2. In each of the 3 groups, SAT, compared with VAT, was more highly correlated with BMI and WC; the correlation between VAT and SAT was weaker compared with the correlations of other combinations; the correlation between BMI and WC was the strongest in JA and Koreans.

**TABLE 2.** Spearman rank correlations among indices of obesity for Japanese American, African American, and Korean men (N = 612)

	$\rho$ ( $p < 0.001$ for all)											
	Japanese Americans (n = 230)				African Americans (n = 91)				Koreans (n = 291)			
	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI
VAT	1.00	0.60	0.73	0.66	1.00	0.66	0.72	0.63	1.00	0.56	0.66	0.64
SAT		1.00	0.83	0.78		1.00	0.93	0.84		1.00	0.74	0.69
WC			1.00	0.89			1.00	0.90			1.00	0.80
BMI				1.00				1.00				1.00

Abbreviations as in Table 1.

### Associations of LDL subfractions with VAT, SAT, WC, and BMI

In each of the 3 groups, VAT was significantly and positively associated with total and small LDL particle concentrations; VAT was significantly and negatively associated with LDL size (Table 3). However, the associations of SAT, WC, and BMI with LDL subfractions were varied among the 3 groups. SAT, WC, and BMI were significantly associated with total and small LDL particle concentrations in JA and Koreans, but no significant associations were found in AA. In JA and Koreans,  $R^2$  values for the associations of indices of obesity with total and small LDL lipoprotein subfractions were different. BMI had the largest  $R^2$  values ( $R^2 = 0.14, 0.12, 0.08,$  and  $0.08$  for BMI, WC, VAT, and SAT) with total LDL particle concentrations. VAT had the largest  $R^2$  values ( $R^2 = 0.14, 0.14, 0.11,$  and  $0.10$  for VAT, WC, BMI, and SAT) with small LDL particle concentrations in JA. However, VAT had the largest  $R^2$  values ( $R^2 = 0.19, 0.10, 0.09,$  and  $0.07$  for VAT, BMI, WC, and SAT with total LDL particle concentrations;  $R^2 = 0.14, 0.06, 0.06,$  and  $0.05$  for VAT, BMI, WC, and SAT with small LDL particle concentrations) in the associations with both total and small LDL particle concentrations in Koreans (Table 3).

### Associations of HDL subfractions with VAT, SAT, WC, and BMI

VAT was significantly and negatively associated with large HDL and HDL size in each of the 3 groups (Table 4). SAT, WC, and BMI were significantly and negatively associated with large HDL concentration and size of HDL in the 3 ethnicities.  $R^2$  values in the association between indices of obesity with HDL lipoprotein subfractions were varied among the ethnicities. For example, VAT had the larger  $R^2$  values in the associations of both large HDL concentration and HDL size compared with those for SAT, WC, and BMI in AA ( $R^2 = 0.22, 0.17, 0.15,$  and  $0.11$  for VAT, BMI, WC, and SAT with large HDL particle concentrations;  $R^2 = 0.15, 0.13, 0.11,$  and  $0.11$  for VAT, WC, BMI, and SAT with HDL size) and in Koreans ( $R^2 = 0.15, 0.14, 0.12,$  and  $0.12$  for VAT, BMI, SAT, and SAT with large HDL particle concentrations;  $R^2 = 0.23, 0.17, 0.16,$  and  $0.12$  for VAT, BMI, WC, and SAT with HDL size). However, WC had

larger  $R^2$  value than BMI, VAT, and SAT did ( $R^2 = 0.19, 0.18, 0.17,$  and  $0.11$  for WC, BMI, VAT, and SAT with large HDL particle concentrations;  $R^2 = 0.29, 0.27, 0.25,$  and  $0.19$  for WC, BMI, VAT, and SAT with HDL size) in JA (Table 4).

### Associations of VLDL subfractions with VAT, SAT, WC, and BMI

In each of the 3 groups, VAT was significantly associated with large VLDL (Table 5). Varied but significant associations of SAT, WC, and BMI with large VLDL were found among the 3 groups. SAT, WC, and BMI were significantly and positively associated with large VLDL in JA and AA, but only BMI was significantly associated with large VLDL in Koreans. SAT, WC, and BMI were variably associated with other VLDL lipoprotein subfractions. In the association with large VLDL, VAT had the largest  $R^2$  value among the indices of obesity in the 3 ethnicities (Table 5).

## DISCUSSION

In the 3 ethnicities of middle-aged men, lipoprotein particle concentrations and size measured by nuclear magnetic resonance spectroscopy were significantly associated with VAT. This result is consistent with our previous results in U.S. white and Japanese middle-aged men [15]. Another study also reported a similar association between lipoprotein and VAT in diabetic patients [25]. We also found that the associations between SAT and lipoprotein subfractions were less strong than the association between VAT and lipoprotein subfractions was.

### Associations of lipoproteins with SAT compared to VAT

Only a few studies have examined the association of lipoprotein particles with SAT versus with VAT. Although it is not completely clear how SAT, compared with VAT, is associated with CHD risk factors, increasing evidence points to weaker associations between SAT and lipoprotein particle concentrations, compared with those associations for VAT. Fox et al. found SAT had a weaker correlation with metabolic factors than VAT in Framingham cohorts [14]. This weaker association with SAT versus VAT was also shown in white and AA patients with type 2 diabetes

**TABLE 3.** Multivariate-adjusted associations between adiposity indices and log-transformed LDL for Koreans, African Americans, and Japanese Americans (N = 612)

	Japanese Americans				African Americans				Koreans						
	B (adjusted-R <sup>2</sup> )		H (adjusted-R <sup>2</sup> )		H (adjusted-R <sup>2</sup> )		H (adjusted-R <sup>2</sup> )		SAT		WC		BMI		
	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI	VAT	SAT	BMI
LDL total	0.26* (0.098)	0.23* (0.083)	0.30* (0.119)	0.33* (0.140)	0.29* (0.071)	0.10 (-0.001)	0.25 (0.052)	0.22 (0.038)	0.44* (0.190)	0.27* (0.069)	0.31* (0.092)	0.33* (0.104)	0.27* (0.059)	0.25* (0.076)	0.27* (0.078)
LDL intermediate	0.17 (0.018)	0.16 (0.016)	0.16 (0.014)	0.17* (0.018)	0.03 (0.033)	-0.04 (0.034)	-0.01 (0.034)	0.02 (0.035)	0.32* (0.104)	0.25* (0.059)	0.27* (0.076)	0.27* (0.078)	0.27* (0.059)	0.25* (0.076)	0.27* (0.078)
LDL large	-0.24* (0.050)	-0.16 (0.020)	-0.19* (0.030)	-0.19* (0.031)	-0.13 (-0.001)	0.06 (-0.014)	0.03 (-0.019)	0.02 (-0.020)	-0.22* (0.045)	-0.06 (0.000)	-0.13 (0.013)	-0.18* (0.030)	-0.06 (0.000)	-0.13 (0.013)	-0.18* (0.030)
LDL small	0.35* (0.139)	0.28* (0.098)	0.35* (0.144)	0.31* (0.114)	0.37* (0.098)	0.23 (0.010)	0.30* (0.050)	0.24 (0.021)	0.38* (0.139)	0.22* (0.045)	0.25* (0.060)	0.24* (0.058)	0.22* (0.045)	0.25* (0.060)	0.24* (0.058)
LDL size	-0.37* (0.150)	-0.28* (0.094)	-0.33* (0.124)	-0.32* (0.114)	-0.31* (0.095)	-0.10 (0.008)	-0.17 (0.029)	-0.16 (0.025)	-0.42* (0.183)	-0.21* (0.048)	-0.28* (0.083)	-0.33* (0.112)	-0.21* (0.048)	-0.28* (0.083)	-0.33* (0.112)

Multiple linear regression model is adjusted for age, pack per year smoking, and alcohol consumption. For the model, the outcome variable is log-transformed lipoprotein concentration or size; primary predictor variable is each index of obesity (VAT, SAT, WC, and BMI). Abbreviations as in Table 1.

\*p < 0.01.

mellitus [25]. Our findings build on the increasing evidence that SAT is less strongly, but significantly, associated with lipoprotein particle concentrations and numbers.

### Associations of triglyceride-rich lipoproteins with VAT

Our findings on the association between indices of obesity and lipoprotein support the hypothesis that VAT has an impact on the altered metabolism of triglyceride-rich lipoprotein. Investigators have tried to explain the mechanism for the associations between indices of obesity and lipoprotein by looking at whether lipoprotein metabolism is influenced by regional body fat, such as VAT, through lipid metabolism in the liver. VAT favors access to the liver, which enhances lipolytic activity in the liver and causes fat accumulation [26]. Then, increased fat in the liver activates cholesterol ester transport protein, which leads to an increased exchange of triglycerides from VLDL to LDL and HDL. Subsequently, the triglyceride-rich LDL and HDL are converted into small and dense LDL and HDL, respectively, by hepatic lipase. In this study, we found that VAT was significantly and positively associated with higher particle concentrations of total and large VLDL and small LDL, as well as significantly inversely associated with large HDL in the 3 ethnicities. We also observed the association of VAT with lower average size of LDL (positively) and HDL (inversely). Our results are consistent with the triglyceride-rich lipoprotein metabolism theory in the 3 ethnicities.

### Associations of triglyceride-rich lipoproteins with WC, BMI, and SAT

We also found similar associations of WC and BMI with large VLDL, small LDL, and lower average size of LDL and HDL as seen in the associations of VAT with triglyceride-rich lipoprotein subfractions in the 3 ethnicities in the associations of SAT, WC, and BMI with triglyceride-rich lipoprotein subfractions. Similar to VAT, SAT, WC, and BMI support the notion that altered metabolism of triglyceride-rich lipoprotein is affected by indices of obesity, except in AA. AA showed significant associations of only WC and BMI with large VLDL, small LDL, and large HDL. SAT did not show significant associations with the triglyceride-rich lipoprotein subfractions in AA. This may be due to the smaller sample size of AA. Another possibility is the difference in fat tissue distribution. Effect of SAT on lipoprotein subfractions appears to be different from that of VAT. The Framingham Heart Study reported that increased SAT was significantly associated with lower triglyceride levels among the individuals who had high VAT, whereas increased SAT was significantly associated with higher triglyceride levels among the individuals who had low VAT [14]. The 3 ethnicities had significantly different fat tissue distributions. Therefore, AA, who had a significantly larger VAT, could explain the different associations between triglyceride-rich lipoprotein subfractions

**TABLE 4.** Multivariate-adjusted associations between adiposity indices and log-transformed HDL for Korean, African American and Japanese American (N = 612)

	Japanese Americans				African Americans				Koreans			
	H (adjusted-R <sup>2</sup> )				H (adjusted-R <sup>2</sup> )				H (adjusted-R <sup>2</sup> )			
	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI	VAT	SAT	WC	BMI
HDL total	-0.10 (0.030)	-0.09 (0.028)	-0.16 (0.048)	-0.16 (0.047)	-0.23 (0.112)	-0.22 (0.104)	-0.23 (0.123)	-0.22 (0.120)	0.15 (0.090)	-0.09 (0.076)	0.01 (0.071)	0.00 (0.071)
HDL large	-0.35* (0.173)	-0.24* (0.106)	-0.38* (0.194)	-0.36* (0.176)	-0.44* (0.218)	-0.31* (0.113)	-0.34* (0.145)	-0.38* (0.173)	-0.36* (0.145)	-0.32* (0.121)	-0.32* (0.117)	-0.35* (0.137)
HDL medium	0.06 (0.008)	-0.05 (0.006)	0.01 (0.005)	-0.02 (0.005)	-0.11 (-0.006)	-0.22 (0.028)	-0.20 (0.023)	-0.23 (0.037)	0.09 (0.038)	0.05 (0.032)	0.05 (0.032)	0.04 (0.031)
HDL small	0.03 (0.002)	0.05 (0.004)	-0.01 (0.002)	0.01 (0.002)	0.01 (-0.009)	0.01 (-0.009)	0.01 (0.000)	0.02 (0.000)	0.33* (0.120)	0.08 (0.017)	0.18* (0.044)	0.17* (0.041)
HDL size	-0.44* (0.254)	-0.35* (0.188)	-0.48* (0.294)	-0.46* (0.273)	-0.36* (0.154)	-0.29* (0.106)	-0.32* (0.125)	-0.29* (0.111)	-0.48* (0.228)	-0.36* (0.124)	-0.41* (0.160)	-0.42* (0.167)

Multiple linear regression model is adjusted for age, pack per year smoking, and alcohol consumption. For the model, the outcome variable is log-transformed lipoprotein concentration or size; primary predictor variable is each index of obesity (VAT, SAT, WC, and BMI). Abbreviations as in Table 1.  
\*p < 0.01.

and SAT. However, further investigations are needed to explain how SAT, WC, and BMI are associated with triglyceride-rich lipoprotein metabolism.

**Study strengths**

We included population-based samples from 3 different ethnicities, which allowed us to look at the cross-ethnic consistency in the associations between each index of obesity and lipoprotein subfractions. The measurements for lipoprotein subfractions and for VAT, SAT, WC, and BMI were standardized across the research centers. This provided higher precision and accuracy in the measurements. In addition, indices of obesity included multiple variables: VAT, SAT, WC, and BMI, from the 3 different ethnic groups. By comparing the associations among the different indices of obesity, this study allowed us to analyze the relative magnitude of associations among the different indices of obesity.

**Study limitations**

The smaller sample size for AA, compared with that of JA and Koreans, gave the associations between indices of obesity and lipoprotein subfractions less statistical power. Although we randomly selected our study samples, our samples may not necessarily be representative of the populations. This also influenced the comparison of the magnitude of associations among the ethnic groups. We measured blood samples only at 1 time point and did not take intraindividual variation [27] into account. Thus, it is possible that the actual difference in lipid variables is smaller than we reported. The study is cross-sectional in design, which prevented the assessment of causality. Clinical significance of those differences among the ethnic groups would be of interest for future studies. Our study included only men and only individuals ages 40 to 49 years. Thus, the results may not be generalizable to other age groups or women.

**CONCLUSIONS**

All 3 ethnic groups showed significant positive associations of VAT with large VLDL and small LDL and a negative association of VAT with large HDL. This study has further expanded the evidence that VAT is significantly associated with both atherogenic and atheroprotective lipoprotein particle concentrations to middle-aged JA, AA, and Korean men. Our results also expanded the evidence that the associations of SAT with lipoprotein subfractions are weaker, compared with those of VAT, in these ethnic groups.

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TABLE 5. Multivariate-adjusted associations between adiposity indices and log-transformed VLDL for Koreans, African Americans, and Japanese Americans (N = 612)

	Japanese Americans						African Americans						Koreans						
	H (adjusted-R <sup>2</sup> )			BMI			H (adjusted-R <sup>2</sup> )			BMI			H (adjusted-R <sup>2</sup> )			BMI			
	VAT	SAT	WC	VAT	SAT	WC	VAT	SAT	WC	VAT	SAT	WC	VAT	SAT	WC	VAT	SAT	WC	
VLDL total	0.19* (0.048)	0.15 (0.034)	0.16 (0.039)	0.19* (0.046)	0.34* (0.093)	0.21 (0.019)	0.15 (-0.004)	0.15 (-0.004)	0.21 (0.019)	0.34* (0.093)	0.21 (0.019)	0.15 (-0.004)	0.15 (-0.004)	0.10 (0.004)	0.10 (0.004)	0.33* (0.102)	0.10 (0.004)	0.14 (0.015)	0.22* (0.042)
VLDL large	0.40* (0.177)	0.25* (0.084)	0.36* (0.150)	0.34* (0.138)	0.44* (0.155)	0.34* (0.070)	0.30* (0.042)	0.30* (0.042)	0.34* (0.070)	0.44* (0.155)	0.34* (0.070)	0.30* (0.042)	0.30* (0.042)	0.19* (0.097)	0.19* (0.097)	0.35* (0.186)	0.19* (0.097)	0.25* (0.121)	0.27* (0.136)
VLDL medium	0.20* (0.055)	0.17 (0.042)	0.16 (0.041)	0.16 (0.038)	0.37* (0.113)	0.21 (0.015)	0.17 (0.004)	0.17 (0.004)	0.21 (0.015)	0.37* (0.113)	0.21 (0.015)	0.17 (0.004)	0.17 (0.004)	0.06 (0.010)	0.06 (0.010)	0.27* (0.079)	0.06 (0.010)	0.09 (0.017)	0.15 (0.031)
VLDL small	-0.03 (-0.014)	0.01 (-0.015)	0.017 (-0.014)	0.06 (-0.011)	0.18 (0.007)	0.10 (-0.013)	0.04 (-0.024)	0.04 (-0.024)	0.10 (-0.013)	0.18 (0.007)	0.10 (-0.013)	0.04 (-0.024)	0.04 (-0.024)	0.07 (-0.005)	0.07 (-0.005)	0.11 (0.002)	0.07 (-0.005)	0.11 (0.002)	0.10 (0.001)
VLDL size	0.30* (0.096)	0.21* (0.052)	0.33* (0.119)	0.28* (0.088)	0.06 (0.017)	0.09 (0.017)	0.06 (0.017)	0.06 (0.017)	0.09 (0.017)	0.06 (0.017)	0.09 (0.017)	0.06 (0.017)	0.06 (0.017)	0.12 (0.057)	0.12 (0.057)	0.20* (0.084)	0.12 (0.057)	0.15 (0.066)	0.16* (0.069)

Multiple linear regression model is adjusted for age, pack per year smoking, and alcohol consumption. For the model, the outcome variable is log-transformed lipoprotein concentration or size; primary predictor variable is each index of obesity (VAT, SAT, WC, and BMI). Abbreviations as in Table 1.

\*p < 0.01.

## REFERENCES

- Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010;121:e46–215.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367:1747–57.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
- Blumenthal RS, Michos ED, Nasir K. Further improvements in CHD risk prediction for women. *JAMA* 2007;297:641–3.
- Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611–9.
- Kathiresan S, Otvos JD, Sullivan LM, et al. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. *Circulation* 2006;113:20–9.
- Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation* 2009;119:931–9.
- Freedman DS, Otvos JD, Jeyarajah EJ, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. *Clin Chem* 2004;50:1189–200.
- Robertson TL, Kato H, Gordon T, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: coronary heart disease risk factors in Japan and Hawaii. *Am J Cardiol* 1977;39:244–9.
- Ding J, Visser M, Kritchevsky SB, et al. The association of regional fat depots with hypertension in older persons of white and African American ethnicity. *Am J Hypertens* 2004;17:971–6.
- Goodpaster BH, Krishnaswami S, Resnick H, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care* 2003;26:372–9.
- Nagaretani H, Nakamura T, Funahashi T, et al. Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance. *Diabetes Care* 2001;24:2127–33.
- Klein S. The case of visceral fat: argument for the defense. *J Clin Invest* 2004;113:1530–2.
- Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007;116:39–48.
- Nakata K, Choo J, Hopson MJ, et al. Stronger associations of sagittal abdominal diameter with atherogenic lipoprotein subfractions than waist circumference in middle-aged US white and Japanese men. *Metabolism* 2010;59:1742–51.
- Kagan A, Harris BR, Winkelstein W Jr, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. *J Chronic Dis* 1974;27:345–64.
- Sekikawa A, Ueshima H, Kadowaki T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in white men in the United States in the post-World War II birth cohort. *Am J Epidemiol* 2007;165:617–24.
- Kagan A, McGee DL, Yano K, Rhoads GG, Nomura A. Serum cholesterol and mortality in a Japanese-American population: the Honolulu Heart program. *Am J Epidemiol* 1981;114:11–20.
- Shin C, Abbott RD, Kim J, Lee H, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study. *J Hum Hypertens* 2004;18:717–23.

20. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313–20.
21. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–16.
22. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol* 1993;3:358–66.
23. Kadowaki T, Sekikawa A, Murata K, et al. Japanese men have larger areas of visceral adipose tissue than Caucasian men in the same levels of waist circumference in a population-based study. *Int J Obes (Lond)* 2006;30:1163–5.
24. Otvos JD. Measurement of lipoprotein subclass profiles by nuclear magnetic resonance spectroscopy. *Clin Lab* 2002;48:171–80.
25. Sam S, Haffner S, Davidson MH, et al. Relationship of abdominal visceral and subcutaneous adipose tissue with lipoprotein particle number and size in type 2 diabetes. *Diabetes* 2008;57:2022–7.
26. Després JP. Is visceral obesity the cause of the metabolic syndrome? *Ann Med* 2006;38:52–63.
27. Marcovina SM, Gaur VP, Albers JJ. Biological variability of cholesterol, triglyceride, low- and high-density lipoprotein cholesterol, lipoprotein(a), and apolipoproteins A-I and B. *Clin Chem* 1994;40:574–8.