Aminotransferase Levels are Associated with Cardiometabolic Risk above and beyond Visceral Fat and Insulin Resistance: The Framingham Heart Study

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Abstract

Objective—We sought to characterize associations between aminotransferase levels and cardiometabolic risk after accounting for visceral adipose tissue (VAT) and insulin resistance.

Methods and Results—Participants (n=2621) from the Framingham Heart Study (mean age 51, 49.8% women) were included. Sex-specific linear and logistic regressions were used to evaluate associations between aminotransferase levels and cardiometabolic risk factors. In multivariable models, increased ALT levels were associated with elevated blood pressure, fasting plasma glucose, and triglycerides and lower HDL levels (all p   0.007). Further, each 1 standard deviation (SD) increase in ALT corresponded to an increased odds of hypertension, diabetes, the metabolic syndrome, impaired fasting glucose, and insulin resistance estimated by HOMA-IR (OR 1.29–1.85, all p   0.002). Associations with ALT persisted after additional adjustment for VAT, insulin resistance, and BMI with the exception of HDL cholesterol in both sexes and blood pressure in women. Results were materially unchanged when moderate drinkers were excluded, when the sample was restricted to those with ALT<40 U/L, and when the sample was restricted to those without diabetes. Similar trends were observed for AST levels, but associations were more modest.

Conclusions—Aminotransferase levels are correlated with multiple cardiometabolic risk factors above and beyond VAT and insulin resistance.

Keywords

liver function tests; obesity; visceral fat; insulin resistance; cardiometabolic risk factors

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Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as the hepatic manifestation of obesity and its metabolic and cardiovascular sequelae [1,2]. Serum aminotransferase levels, particularly alanine aminotransferase (ALT), may be used to estimate NAFLD in obese and nonobese individuals [3,4], and serum ALT appears to be the

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liver enzyme most closely related to liver fat content [5]. Elevated ALT levels have been associated with metabolic risk factors for cardiovascular disease, including type 2 diabetes mellitus and the metabolic syndrome [6–9]. Such associations raise the possibility that NAFLD, obesity, and metabolic derangements may share a common pathogenesis. They also raise the possibility that serum aminotransferase levels may be useful indicators of cardiometabolic risk above and beyond adiposity and insulin resistance.

The goal of the present study was to explore the association between serum aminotransferase levels and metabolic risk factors for cardiovascular disease in a community-based sample unselected for NAFLD, obesity, or metabolic disease. We tested the hypothesis that aminotransferase levels are associated with cardiometabolic risk above and beyond generalized and central adiposity and insulin resistance. We also tested this hypothesis among those with both elevated and normal aminotransferase levels.

Methods

Study Sample

Subjects were drawn from the Framingham Heart Study, a prospective cohort study that began with 5,209 residents of Framingham, Massachusetts in 1948. In 1971, the offspring and spouses of the original cohort were enrolled in the Offspring Study, and in 2002 the children of the original cohort's offspring were enrolled in the Third Generation Study. Between June 2002 and April 2005, 3,529 Offspring and Third Generation participants were enrolled in the Multi-Detector Computed Tomography (MDCT) substudy and underwent chest and abdominal computed tomographic (CT) scanning. The current study sample consisted of the 2,621 participants (1,305 women and 1,316 men) who had interpretable abdominal CT scans and a complete covariate profile. The institutional review boards of the Boston University Medical Center and Massachusetts General Hospital approved the study protocol. All subjects provided informed written consent.

Multidetector CT Scan Protocol and Measurement of VAT and SAT

Participants underwent eight-slice multidetector abdominal CT scanning in a supine position (LightSpeed Ultra, General Electric, Milwaukee, WI). Twenty-five contiguous 5-mm thick slices (120 kVp, 400 mA, gantry rotation time 500 ms, and table feed 3:1) were obtained, covering 125 mm above the level of S1. VAT and SAT volumes were quantified from CT scans using a semiautomatic segmentation technique at a dedicated offline workstation (Aquarius 3D Workstation; TeraRecon, San Mateo, CA). A reader manually traced the abdominal muscular wall separating the two layers. An image display window width of −195 to −45 Hounsfield units and a window center of −120 Hounsfield units were used to identify pixels containing fat. VAT was defined as adipose tissue inside the abdominal muscular wall and SAT as adipose tissue outside the abdominal muscular wall. Interclass correlations for inter-reader comparisons were 0.997 for SAT and 0.992 for VAT on a random sample of 100 scans; high intra-reader correlations were similarly obtained.

Baseline Measurements and Definitions

Serum ALT and AST levels were measured on fasting morning samples using the kinetic method (Beckman Liquid-Stat Reagent Kit) [10]. Coefficients of variation were 4.1–4.4% and 3.8–4.5% for ALT and AST, respectively.

Covariates and Risk Factor Assessment

Risk factors used in this study were measured at the seventh Framingham Offspring examination (1998–2001) and the first Third Generation examination (2002–2005). BMI was calculated as weight in kilograms divided by the square of height in meters. Waist

circumference was measured at the umbilicus. Serum triglycerides, HDL cholesterol, and fasting plasma glucose were measured in fasting morning samples from participants. Diabetes was defined as fasting plasma glucose   126 mg/dl or treatment with a hypoglycemic agent or insulin; impaired fasting glucose was defined as a fasting plasma glucose level of 100–125 mg/dl in the absence of diabetes treatment. Hypertension was defined as systolic blood pressure   140 mmHg and diastolic blood pressure as   90 mmHg or antihypertensive treatment. Current smoking was defined as smoking   1 cigarette per day in the past year. Alcohol use was evaluated through a physician-administered questionnaire and patients were considered to have high alcohol intake if they reported more than 14 drinks per week (men) or 7 drinks per week (women). Women were classified as postmenopausal if periods had stopped for   1 year. Metabolic syndrome was defined by modified Adult Treatment Panel III criteria (impaired fasting glucose defined as fasting plasma glucose 100–125 mg/dl in the absence of treatment of diabetes, the high triglyceride component was defined as triglycerides   150 mg/dl or treatment with a lipid-lowering agent, and blood pressure criteria were modified to include treatment for hypertension). Insulin resistance was defined as having greater than the top quartile of the homeostasis model assessment of insulin resistance (HOMA-IR) (fasting glucose × fasting insulin/22.5) distribution among individuals without diabetes by sex [11] (for the analysis sample, > 3.06 for women and > 3.51 for men).

Statistical Analysis

ALT and AST were natural log-transformed to normalize their skewed distribution. Sex-specific, age-adjusted Pearson correlations between log ALT and log AST levels were calculated with adiposity traits and cardiometabolic risk factors.

Multivariable linear and logistic regression models were used to assess the significance of covariate-adjusted associations between aminotransferase levels and continuous and dichotomous cardiometabolic risk factors, respectively. The increment in covariate-adjusted risk factors per 1-SD increase in log ALT and log AST was estimated for continuous variables while the odds ratio of the risk factor per 1-SD increase in log aminotransferase level was estimated for dichotomous variables. Covariates included age, current smoking, high alcohol intake (>14 drinks/week for men or >7 drinks/week for women), physical activity, menopausal status (women only), and hormone replacement therapy (women only). For models of systolic and diastolic blood pressure, fasting plasma glucose, HDL cholesterol, and log triglycerides, an additional covariate of treatment for hypertension, diabetes, or lipid disorders, respectively, was included. Finally, additional models evaluated the impact of the associations after additional adjustment for VAT, HOMA-IR (where appropriate), and BMI (separately).

In secondary analyses, we restricted the sample to those with aminotransferase levels in the normal range (ALT<40 U/L or AST<40 U/L, respectively), to participants not reporting high alcohol intake (7 drinks per week [women] or   14 drinks per week [men]), and to individuals without diabetes.

Further, age-adjusted rates of CVD risk factors were calculated within tertiles of ALT stratified by tertiles of VAT and a test of trend (also age-adjusted) across ALT tertile levels within each VAT tertile was performed. Given the greater number and strength of associations between ALT and cardiometabolic risk factors than between AST and cardiometabolic risk factors, the analysis was only performed with ALT.

SAS version 9.2 was used to perform all computations. A 2-tailed p-value <0.05 was considered significant.

Results

Study Sample Characteristics

The characteristics of the study sample are summarized in Table 1. The mean age of study participants was 52 years for women and 50 years for men; 49.8% of participants were women. Mean ALT and AST levels were 20.4 U/L (SD 12.5) and 21.4 U/L (SD 8.5) in women and 31.2 U/L (SD 22.8) and 26.0 U/L (SD 15.9) in men, respectively.

Correlations Between Aminotransferase Levels and Cardiometabolic Risk Factors

Increasing log ALT levels were associated with most cardiometabolic risk factor levels in women and men after adjusting for age (Table 2). More specifically, higher levels of log ALT were associated with higher levels of SAT, VAT, waist circumference, BMI, log triglycerides, serum fasting glucose, insulin resistance, systolic and diastolic blood pressure and with lower HDL cholesterol. Correlations between log AST and risk factors showed similar trends as observed in ALT, but associations were attenuated and fewer significant correlations were observed. Higher log AST levels were correlated with higher diastolic blood pressure, and greater insulin resistance in men and women and additionally with increased BMI, waist circumference, systolic blood pressure, and VAT in men.

Multivariable-Adjusted Models

In multivariable adjusted models, log ALT levels were associated with systolic and diastolic blood pressure in both sexes. Among women, SBP was on average 1.19 mm Hg higher per 1-SD increase in log ALT (p=0.007) and among men, SBP was 2.07 mm Hg higher on average per 1-SD increase in log ALT (p<0.0001), after covariate adjustment. This association was attenuated slightly but persisted in men after additional adjustment for VAT, insulin resistance, and BMI (separately) and persisted in women after adjustment for insulin resistance, but significance was lost after adjustment for VAT and for BMI. Associations between DBP and log ALT levels remained significant in both sexes after adjustments for VAT, IR, and BMI (Table 3).

Fasting plasma glucose was associated with ALT level in both men and women; these associations persisted after additional adjustments for VAT, IR, and BMI.

For each 1-SD increase in log ALT, HDL was 1.4 mg/dL lower in women (p=0.001) and 1.1 mg/dL lower in men (p=0.002); however, these associations did not persist after additional adjustment for VAT, IR, or BMI. For each 1-SD increase in log ALT, log triglycerides were 0.08 mg/dL higher in women (p<0.0001) and 0.12 mg/dL higher in men (p<0.0001). These associations remained significant with slight attenuation in both sexes after adjustment for VAT, IR, and BMI.

Associations between log ALT and dichotomous traits were fairly strong (all OR > 1.29, all p ≤ 0.0002) and generally persisted after adjustment for VAT, BMI, and HOMA-IR. For example, for every 1-SD increase in log ALT, the odds ratio of metabolic syndrome was 1.61 times higher in women and 1.72 times higher in men. These relations remained significant after adjustment for VAT, IR, and BMI.

Far fewer significant associations were observed between log AST and cardiometabolic risk factors than between log ALT and risk factors (Table 4). Of the risk factors tested, only DBP and HDL were significantly associated with AST level in both men and women before and after additional adjustment for VAT, IR, and BMI.

Associations between ALT and AST and cardiometabolic risk factors were generally similar between men and women, and sex interactions were generally negative (Tables 3 and 4).

Secondary Analyses

Secondary analyses excluded participants with high alcohol intake (>7 drinks per week [women], >14 drinks per week [men], n = 394), participants with diabetes (n = 159), and participants with ALT levels above the normal range (40 U/L, n = 322), respectively. When moderate drinkers were excluded from the analysis, results were essentially unchanged (data not shown). Among individuals without diabetes, there was attenuation of the effect size of the association between log ALT and fasting glucose level (beta coefficient 1.79 to 1.22 [women], beta coefficient 2.75 to 1.38 [men], all p-values <0.0001) and between log ALT and HOMA-IR (beta coefficient 0.41 to 0.33 [women], beta coefficient 0.48 to 0.38 [men], all p-values <0.0001); other associations were materially unchanged and persisted after additional adjustment for VAT, IR, and BMI (data not shown). When multivariable and logistic regressions were simultaneously adjusted for BMI, VAT, and HOMA-IR (with the exception of glycemic traits, which were not adjusted for HOMA-IR, and HOMA-IR, which was not adjusted for glucose), results were not appreciably different (data not shown).

When the sample was limited to those with ALT levels in the normal range (<40 U/L), significant associations persisted without attenuation of effect size (supplementary table). Of note, the odds of impaired fasting glucose was similar for each 1-SD increase in log ALT for both men and women in the normal range ALT sample (OR 1.44, p=0.0001 [women], OR 1.62, p<0.0001[men]) relative to the study population as a whole (OR 1.30, p=0.0002 [women], OR 1.29, p<0.0001 [men]). These associations persisted after additional adjustment for VAT and BMI. Among women with ALT in the normal range, the odds of the metabolic syndrome per 1-SD increase in log ALT was increased relative to the entire sample (OR 1.78, p<0.0001 versus 1.61, p<0.0001). This relationship remained after adjustment for VAT, insulin resistance, and BMI. Among men with ALT in the normal range, the effect sizes of each 1-SD increase in log ALT on SBP and DBP were increased relative to the entire sample.

Combination of log ALT and VAT

Age-adjusted rates of cardiometabolic risk factors within tertiles of ALT stratified by tertiles of VAT are shown in the figure. In women and men, the age-adjusted prevalence of diabetes, impaired fasting glucose (IFG), hypertension, and metabolic syndrome (MetS) increased across increasing tertiles of VAT. Of note, rates of these risk factors also increased across increasing ALT tertiles in the higher VAT tertiles for both sexes.

Discussion

Principal Findings

Our results demonstrate a robust association between serum alanine aminotransferase levels and multiple cardiometabolic risk factors in a community-based sample. The most important finding in our study is the strong association between serum ALT level and cardiometabolic risk after adjustment for visceral adipose tissue and insulin resistance. These associations remained significant when participants reporting moderate alcohol intake (>7 drinks per week [women], >14 drinks per week [men]) and those with diabetes were excluded from the analysis. In addition, among those with serum ALT in the normal range (<40 U/L), the associations of log ALT and cardiometabolic risk factors remained significant after multivariable adjustment. These findings suggest that serum ALT levels are associated with cardiometabolic risk independent of visceral adiposity and insulin resistance and that even modest elevations in ALT that fall in the "normal range" may be a clinically significant precursor to cardiometabolic disease.

In the Context of Current Literature

Multiple studies have linked NAFLD with metabolic risk factors for cardiovascular disease, including type 2 diabetes mellitus and the metabolic syndrome, in a variety of populations [6–9,12,13]. The majority of individuals with NAFLD are overweight or obese or have type 2 diabetes, but NAFLD is associated with insulin resistance in normal weight individuals without diabetes [14]. This suggests that NAFLD may be an early predictor of metabolic disease that is distinct from other adiposity traits. Many studies have adjusted for easily measurable adiposity traits such as waist circumference and BMI. In a small study of male subjects, Targher et al. [15] found that nonalcoholic steatohepatitis (NASH) was predictive of an atherogenic biomarker profile independent of visceral adiposity, as measured by ultrasound. This finding suggests that fat in the liver may confer CVD risk beyond that associated with more generalized obesity. Previous work from the Framingham Heart Study found that fatty liver as measured by CT is associated with lipid and glucose traits independent of VAT [16]. Our results extend these findings to show that serum ALT levels, as surrogate biomarkers of NAFLD, are also associated with cardiometabolic risk factors independent of VAT. In addition, we show that ALT levels are associated with metabolic risk independent of BMI and insulin resistance.

Many studies using aminotransferase levels to examine the link between NAFLD and cardiometabolic risk have considered 40 U/L as the upper limit of normal for both ALT and AST. These values were derived from the mean + 2 SD in a "healthy referent sample" from the 1950s [17]. More recently, some have issued calls to adjust normal ALT values on the basis of sex and BMI [18,19]. Prati et al [20] found that lowering the upper limit of normal ALT levels to 30 U/L in men and 19 U/L in women would increase the sensitivity of liver injury detection from 55% to 76%, mostly due to increased detection of fatty liver. The presence of histological damage from NAFLD in the context of normal ALT levels has also been observed [21,22]. Our finding that serum ALT levels <40 U/L are strongly associated with cardiometabolic risk suggests that ALT levels represent a continuum of risk rather than a cutoff below which can be considered healthy and that even subtle ALT elevations may be clinically relevant.

Potential Mechanisms

There are several possible mechanisms linking NAFLD, NASH, and cardiometabolic risk. A "2-hit" hypothesis of lipid accumulation in hepatocytes in the presence of hepatic insulin resistance and has been proposed to explain the development of NAFLD and NASH [23]. Intrahepatic fatty acid accumulation results mostly from the lipolysis of abdominal adipose tissue, but also from dietary chylomicrons and de novo lipogenesis in the liver [24,25]. The relative contributions of fat in the liver versus other fat depots to cardiometabolic risk is not entirely clear. Previous work from the Framingham Heart Study found that both fatty liver and VAT are associated with cardiometabolic risk [16,26]. Fabbrini et al. found that fatty liver, but not VAT, is associated with metabolic abnormalities [27], while work from the Jackson Heart Study found that fatty liver and VAT were independently associated with cardiometabilic risk, but that associations with triglycerides and HDL cholesterol were stronger for VAT than fatty liver[28].

Secretion by adipose tissue of adipokines, such as adiponectin, leptin, and resistin, may play a role in the development of NAFLD and other cardiometabolic abnormalities [29–31]. For example, patients with NAFLD have reduced levels of adiponectin [32], a hormone with anti-inflammatory and anti-fibrotic properties, lower levels of which have been associated with cardiometabolic risk [33,34]. In addition, the liver is the site of production for biomarkers of inflammation and endothelial dysfunction, including C-reactive protein (CRP), fibrinogen,

and plasminogen activator inhibitor-1 (PAI-1) all of which are elevated in fatty liver disease and which are considered biomarkers of CVD risk [15,31].

Our findings showed a greater number and strength of associations between ALT and cardiometabolic risk factors than between AST and cardiometabolic risk factors. This is likely due to the stronger association of ALT with NAFLD [35] and obesity [36]. It may also reflect the greater specificity of ALT for liver injury since ALT is restricted to hepatocytes while AST is also released from the heart, skeletal muscle, kidney, brain, pancreas, and red blood cells [37].

Strengths and Limitations

Compared with prior work on aminotransferase levels and cardiometabolic risk, the strengths of the present study include a large population-based sample not selected for NAFLD, obesity, or metabolic disease with rich covariate data, including VAT. The richness of the covariate data allows us to adjust for several important confounders in exploring the association between aminotransferase levels and cardiometabolic risk and to further adjust for visceral adiposity and insulin resistance. We were able to conduct these analyses in a sample that included participants with normal and elevated aminotransferase levels.

Some limitations deserve mention. First, this study is cross-sectional and observational, so we are unable to assess temporality and causality. Second, we relied on a single measurement of aminotransferase levels for each participant, so we were unable to account for inter-individual variation in these levels. Such variability, however, is likely to bias our results towards the null hypothesis, and is unlikely to account for our significant findings. We were also unable to exclude individuals with non-NAFLD liver disease such as viral hepatitis or drug-induced liver injury as the cause of aminotransferase elevations, although the absolute numbers of such conditions are likely to be low in our community-based population study. We were unable to separate out the retroperitoneal VAT compartment in our analyses. Waist circumference measured at the umbilicus can be problematic in those with a pendulant abdomen. Participants taking metformin were classified as having diabetes, although they might have been taking the medication for other reasons. We made use of surrogate markers for both insulin resistance using the HOMA-IR and NAFLD using serum aminotransferase levels, which are insensitive for detecting NAFLD, NASH, advanced fibrosis, and cirrhosis. Finally, our sample is comprised of Caucasians, which limits the generalizability of our results to other populations or ethnic groups.

Conclusions

Serum ALT levels, including those in the normal range, are associated with cardiometabolic risk above and beyond visceral fat and insulin resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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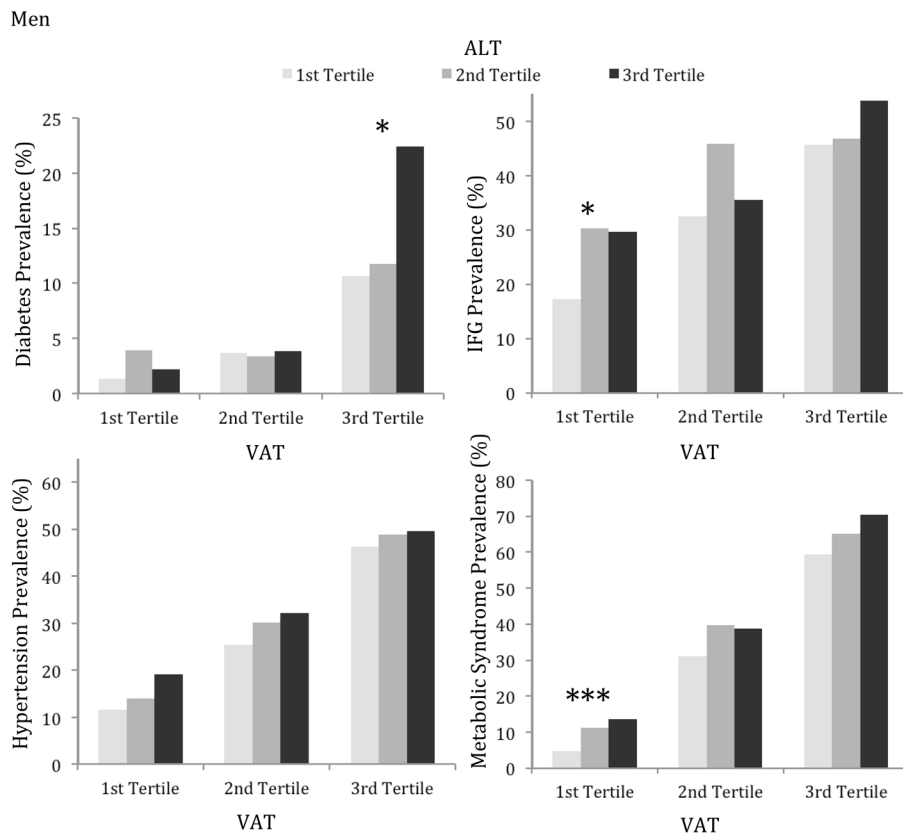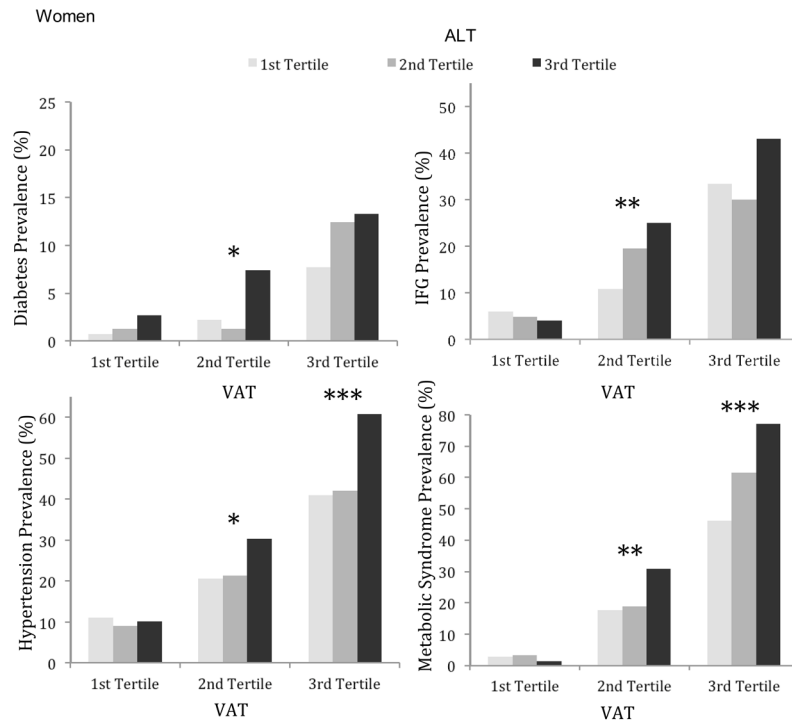
Women

ALT

Figure.

Age-adjusted prevalence of diabetes mellitus, impaired fasting glucose (IFG), hypertension, and metabolic syndrome by tertiles of ALT within tertiles of VAT. Results are shown for women (top) and men (bottom). Significant p-values for trend across ALT tertiles within each VAT tertile are designated by *p<0.05, **p<0.01, ***p<0.001.

Table 1

Study Sample Characteristics

	Women (N=1305)	Men (N=1316)
Age (years)	52.2 (9.8)	49.7 (10.7)
Postmenopausal (%)	52.2	NA
Hormone Replacement (%)	19.6	NA
Current Smoking (%)	11.2	13.5
High Alcohol Intake* (%)	14.1	16.0
Body Mass Index (kg/m^2)	27.2 (5.7)	28.2 (4.4)
Waist Circumference (cm)	93.7 (15.2)	100.4 (11.5)
Visceral Adipose Tissue (cm^3)	1396.2 (834.5)	2210.0 (1011.9)
Subcutaneous Adipose Tissue (cm^3)	3187.4 (1480.0)	2576.3 (1168.0)
Systolic Blood Pressure (mm Hg)	120.5 (17.5)	123.2 (14.7)
Diastolic Blood Pressure (mm Hg)	73.8 (9.1)	77.9 (9.0)
Hypertension (%)	27.5	30.7
Hypertension Treatment (%)	19.4	18.6
Triglycerides (mg/dl)[†]	97 (69–142)	116 (78–174)
HDL Cholesterol (mg/dl)	60.5 (16.1)	45.6 (12.2)
Lipid Treatment (%)	10.3	17.6
Fasting Glucose (mg/dl)	96.1 (17.4)	101.6 (21.3)
Impaired Fasting Glucose [‡] (%)	19.7	37.5
HOMA-IR[†]	2.4 (2.0–3.3)	2.8 (2.3–3.8)
Insulin Resistance (%)	29.2	28.3
Diabetes (%)	5.4	6.7
Diabetes Treatment (%)	3.0	3.3
Metabolic Syndrome (%)	29.0	37.0
ALT (U/L)[†]	18 (14–23)	26 (20–36)
AST (U/L)[†]	20 (17–24)	23 (20–29)
Physical Activity Score	20.0 (17.0–24.0) 36.8 (5.9)	38.5 (8.2)

Data are presented as the mean (standard deviation) for continuous traits, and percentage having that characteristic (n/N) for categorical data.

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*
>7 drinks/week in women, >14 drinks/week in men.

†Median with 25th–75th percentiles.

‡Fasting plasma glucose 100 to 125 mg/dL and not on diabetes treatment.

Table 2

Sex-specific Pearson Correlation Coefficients between log ALT and log AST and Cardiometabolic Risk Factors, Age-Adjusted

	Log ALT		Log AST	
	Women	Men	Women	Men
Age	0.04	−0.29 ****	0.10 ***	−0.12 ****
Body Mass Index	0.20 ****	0.26 ****	0.01	0.10 ***
Waist Circumference	0.22 ****	0.25 ****	0.03	0.07 *
Visceral Adipose Tissue	0.21 ****	0.31 ****	0.01	0.10 ***
Subcutaneous Adipose Tissue	0.17 ****	0.18 ****	0.01	0.05
Systolic Blood Pressure	0.11 ****	0.16 ****	0.05	0.08 **
Diastolic Blood Pressure	0.13 ****	0.21 ****	0.08 **	0.12 ****
Log Triglycerides	0.16 ****	0.20 ****	0.01	0.04
HDL Cholesterol	−0.10 ***	−0.07 *	0.07 **	0.08 **
Fasting Glucose	0.17 ****	0.14 ****	0.04	0.03
Log HOMA-IR	0.28 ****	0.27 ****	0.07 **	0.07 *

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance.

*
p<0.05;

**
p<0.01;

***
p<0.001;

****
p<0.0001

Table 3

Sex-Specific Multivariable-Adjusted [*] Regressions for ALT with Cardiometabolic Risk Factors

	Women		Men		
	MV adjusted beta coefficient or OR (95% CI)	p-value	MV adjusted beta coefficient or OR (95% CI)	p-value	p-value for sex interaction
Continuous Variables					
Systolic Blood Pressure					
Base Model [*]	1.19 (0.33, 2.06)	0.007	2.07 (1.29, 2.84)	<0.0001	0.21
+VAT	0.48 (−0.37, 1.33)	0.27	1.42 (0.62, 2.22)	0.0005	
+HOMA-IR	0.91 (0.03, 1.78)	0.04	1.89 (1.10, 2.67)	<0.0001	
+BMI	0.55 (−0.30, 1.40)	0.20	1.44 (0.65, 2.23)	0.0004	
Diastolic Blood Pressure					
Base Model [*]	0.94 (0.45, 1.43)	0.0002	1.86 (1.37, 2.36)	<0.0001	0.046
+VAT	0.58 (0.09, 1.07)	0.02	1.37 (0.86, 1.88)	<0.0001	
+HOMA-IR	0.86 (0.36, 1.37)	0.0008	1.76 (1.25, 2.26)	<0.0001	
+BMI	0.61 (0.12, 1.10)	0.02	1.44 (0.94, 1.94)	<0.0001	
Fasting Plasma Glucose					
Base Model [*]	1.79 (1.02, 2.55)	<0.0001	2.75 (1.71, 3.79)	<0.0001	0.48
+VAT	0.82 (0.09, 1.55)	0.03	2.00 (0.92, 3.08)	0.0003	
+BMI	0.99 (0.25, 1.73)	0.01	1.82 (0.76, 2.88)	0.0008	
Log Triglycerides					
Base Model [*]	0.08 (0.06, 0.11)	<0.0001	0.12 (0.09, 0.15)	<0.0001	0.06
+VAT	0.04 (0.02, 0.07)	0.001	0.07 (0.04, 0.10)	<0.0001	
+HOMA-IR	0.05 (0.03, 0.08)	0.0001	0.09 (0.06, 0.12)	<0.0001	
+BMI	0.05 (0.03, 0.08)	<0.0001	0.09 (0.06, 0.12)	<0.0001	
HDL Cholesterol					
Base Model [*]	−1.40 (−2.26, −0.55)	0.001	−1.05 (−1.71, −0.38)	0.002	0.10
+VAT	−0.29 (−1.11, 0.53)	0.49	0.16 (−0.50, 0.82)	0.63	
+HOMA-IR	−0.56 (−1.41, 0.28)	0.19	−0.45 (−1.11, 0.20)	0.18	
+BMI	−0.50 (−1.33, 0.33)	0.23	−0.23 (−0.90, 0.44)	0.50	
HOMA-IR					0.76

	Women		Men		
	MV adjusted beta coefficient or OR (95% CI)	p-value	MV adjusted beta coefficient or OR (95% CI)	p-value	p-value for sex interaction
Base Model*	0.41 (0.31, 0.51)	<0.0001	0.48 (0.35, 0.61)	<0.0001	
+VAT	0.23 (0.15, 0.32)	<0.0001	0.22 (0.09, 0.34)	0.0007	
+BMI	0.26 (0.17, 0.35)	<0.0001	0.21 (0.09, 0.33)	0.0006	
Dichotomous Variables					
Hypertension					0.75
Base Model*	1.37 (1.20, 1.57)	<0.0001	1.34 (1.17, 1.54)	<0.0001	
+VAT	1.22 (1.06, 1.40)	0.005	1.16 (1.00, 1.33)	0.04	
+HOMA-IR	1.21 (1.05, 1.39)	0.01	1.26 (1.09, 1.44)	0.002	
+BMI	1.25 (1.09, 1.43)	0.002	1.20 (1.04, 1.38)	0.01	
IFG					0.52
Base Model*	1.30 (1.13, 1.49)	0.0002	1.29 (1.14, 1.45)	<0.0001	
+VAT	1.14 (0.99, 1.32)	0.07	1.14 (1.01, 1.30)	0.04	
+BMI	1.17 (1.02, 1.36)	0.03	1.19 (1.05, 1.35)	0.006	
Diabetes					0.40
Base Model*	1.62 (1.30, 2.03)	<0.0001	1.42 (1.14, 1.77)	0.002	
+VAT	1.48 (1.17, 1.87)	0.001	1.27 (1.01, 1.60)	0.04	
+BMI	1.50 (1.18, 1.92)	0.001	1.23 (0.97, 1.54)	0.08	
Metabolic Syndrome					0.74
Base Model*	1.61 (1.41, 1.84)	<0.0001	1.72 (1.50, 1.96)	<0.0001	
+VAT	1.33 (1.15, 1.55)	0.0002	1.29 (1.11, 1.49)	0.0006	
+HOMA-IR	1.26 (1.09, 1.47)	0.002	1.43 (1.24, 1.65)	<0.0001	
+BMI	1.42 (1.23, 1.64)	<0.0001	1.41 (1.22, 1.64)	<0.0001	
Insulin Resistance					0.65
Base Model*	1.68 (1.47, 1.91)	<0.0001	1.91 (1.66, 2.20)	<0.0001	
+VAT	1.42 (1.23, 1.65)	<0.0001	1.51 (1.30, 1.75)	<0.0001	
+BMI	1.49 (1.29, 1.72)	<0.0001	1.61 (1.38, 1.89)	<0.0001	

Data presented include effect size (SE) expressed per 1 SD increase in log ALT for continuous data, and the odds of the condition per 1 SD increase in log ALT with 95% confidence intervals for dichotomous data.

*
Adjusted for age, current smoking, high alcohol intake, physical activity, and menopausal status (women only), hormone replacement therapy (women only); for blood pressure, FPG, HDL cholesterol, and log triglycerides, an additional covariate of treatment for HTN, diabetes, or lipid disorders, respectively, was included.

Abbreviations: VAT, visceral adipose tissue; HOMA-IR, homeostasis model of insulin resistance; BMI, body mass index; HDL, high-density lipoprotein; IFG, impaired fasting glucose.

Table 4

Sex-Specific Multivariable-Adjusted * Regressions for AST with Cardiometabolic Risk Factors

	Women		Men		
	MV adjusted beta coefficient or OR (95% CI)	p-value	MV adjusted beta coefficient or OR (95% CI)	p-value	p-value for sex interaction
Continuous Variables					
Systolic Blood Pressure					0.57
Base Model *	0.39 (−0.47, 1.26)	0.37	0.88 (0.13, 1.63)	0.02	
+VAT	0.45 (−0.39, 1.29)	0.29	0.65 (−0.09, 1.40)	0.09	
+HOMA-IR	0.34 (−0.52, 1.20)	0.44	0.81 (0.06, 1.57)	0.03	
+BMI	0.44 (−0.40, 1.28)	0.30	0.63 (−0.11, 1.37)	0.10	
Diastolic Blood Pressure					0.40
Base Model *	0.54 (0.05, 1.04)	0.03	0.99 (0.50, 1.47)	<0.0001	
+VAT	0.57 (0.09, 1.05)	0.02	0.81 (0.34, 1.29)	0.0008	
+HOMA-IR	0.52 (0.03, 1.02)	0.04	0.94 (0.46, 1.43)	0.0001	
+BMI	0.57 (0.08, 1.05)	0.02	0.81 (0.34, 1.29)	0.0008	
Fasting Plasma Glucose					0.23
Base Model *	0.09 (−0.68, 0.86)	0.82	1.20 (0.19, 2.21)	0.02	
+VAT	0.08 (−0.64, 0.80)	0.82	0.91 (−0.10, 1.91)	0.08	
+BMI	0.08 (−0.65, 0.81)	0.83	0.79 (−0.20, 1.79)	0.12	
Log Triglycerides					0.50
Base Model *	0.01 (−0.02, 0.03)	0.62	0.02 (−0.01, 0.05)	0.19	
+VAT	0.01 (−0.02, 0.03)	0.58	0.00 (−0.03, 0.03)	0.77	
+HOMA-IR	0.00 (−0.03, 0.03)	0.98	0.01 (−0.02, 0.04)	0.42	
+BMI	0.01 (−0.02, 0.03)	0.62	0.01 (−0.02, 0.04)	0.61	
HDL Cholesterol					0.46
Base Model *	1.25 (0.39, 2.11)	0.004	0.68 (0.04, 1.32)	0.04	
+VAT	1.24 (0.44, 2.05)	0.002	1.04 (0.43, 1.65)	0.0008	
+HOMA-IR	1.43 (0.60, 2.26)	0.0007	0.84 (0.22, 1.46)	0.008	
+BMI	1.26 (0.44, 2.08)	0.003	0.98 (0.35, 1.60)	0.002	
HOMA-IR					0.90

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	Women		Men		
	MV adjusted beta coefficient or OR (95% CI)	p-value	MV adjusted beta coefficient or OR (95% CI)	p-value	p-value for sex interaction
Base Model [*]	0.10 (0.00, 0.20)	0.049	0.13 (0.01, 0.26)	0.04	
+VAT	0.09 (0.01, 0.18)	0.04	0.05 (−0.07, 0.17)	0.41	
+BMI	0.09 (0.01, 0.18)	0.04	0.03 (−0.08, 0.15)	0.56	0.39
Dichotomous Variables					
Hypertension					
Base Model [*]	1.23 (1.08, 1.41)	0.002	1.13 (1.00, 1.28)	0.05	
+VAT	1.23 (1.07, 1.41)	0.003	1.09 (0.96, 1.23)	0.21	
+HOMA-IR	1.19 (1.04, 1.37)	0.01	1.11 (0.98, 1.26)	0.11	
+BMI	1.25 (1.09, 1.43)	0.002	1.09 (0.96, 1.24)	0.19	0.77
IFG					
Base Model [*]	1.01 (0.88, 1.17)	0.85	1.08 (0.97, 1.22)	0.16	
+VAT	1.00 (0.87, 1.15)	0.98	1.04 (0.93, 1.17)	0.46	
+BMI	1.01 (0.87, 1.16)	0.91	1.05 (0.94, 1.18)	0.39	0.40
Diabetes					
Base Model [*]	1.14 (0.89, 1.46)	0.31	1.00 (0.80, 1.25)	0.98	
+VAT	1.16 (0.92, 1.47)	0.21	0.97 (0.78, 1.21)	0.79	
+BMI	1.16 (0.91, 1.48)	0.23	0.96 (0.78, 1.18)	0.70	0.78
Metabolic Syndrome					
Base Model [*]	1.11 (0.98, 1.26)	0.11	1.16 (1.03, 1.30)	0.01	
+VAT	1.09 (0.94, 1.27)	0.24	1.07 (0.93, 1.22)	0.34	
+HOMA-IR	1.03 (0.89, 1.19)	0.72	1.12 (0.98, 1.28)	0.11	
+BMI	1.13 (0.98, 1.30)	0.10	1.08 (0.94, 1.24)	0.28	0.49
Insulin resistance					
Base Model [*]	1.12 (0.99, 1.27)	0.07	1.22 (1.08, 1.38)	0.001	
+VAT	1.11 (0.97, 1.29)	0.14	1.15 (1.00, 1.32)	0.04	
+BMI	1.14 (0.97, 1.31)	0.07	1.15 (1.00, 1.33)	0.051	

Data presented include effect size (SE) expressed per 1 SD increase in log AST for continuous data, and the odds of the condition per 1 SD increase in log AST with 95% confidence intervals for dichotomous data.

*
Adjusted for age, current smoking, high alcohol intake, physical activity, and menopausal status (women only), hormone replacement therapy (women only); for blood pressure, FPG, HDL cholesterol, and log triglycerides, an additional covariate of treatment for HTN, diabetes, or lipid disorders, respectively, was included.

Abbreviations: VAT, visceral adipose tissue; HOMA-IR, homeostasis model of insulin resistance; BMI, body mass index; HDL, high-density lipoprotein; IFG, impaired fasting glucose.