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Trunk Fat is Associated with Increased Serum Levels of Alanine Aminotransferase in the US

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Abstract

Background & Aims—Liver injury is associated with obesity and related measures such as body mass index (BMI) and waist circumference. The relationship between liver injury and body composition has not been evaluated in a population-based study.

Methods—Using data from a US population-based survey, we examined the contributions of body composition, measured by dual-energy x-ray absorptiometry (DXA), to increased serum alanine aminotransferase (ALT) activity among 11,821 adults without viral hepatitis. Trunk fat, extremity fat, trunk lean, and extremity lean mass were divided by height squared and used to categorize subjects into quintiles; logistic regression odds ratios (OR) were calculated for increased ALT.

Results—Increased ALT was associated with higher measures of fat and lean mass ($p < 0.001$) after adjustment for alcohol consumption and other liver injury risk factors in separate models for each DXA measure. Trunk fat was associated with increased ALT ($p \leq 0.001$) in models also including any 1 of the other 3 measures. Extremity fat was independently inversely associated among women ($p < 0.001$). Trunk and extremity lean mass were not independently related to increased ALT. In models that contained all 4 DXA measures, the OR (95% confidence interval) for increased ALT for the highest, relative to lowest, quintile of trunk fat/height squared was 13.8 (5.4–35.3) for men and 7.8 (3.9–15.8) for women. When BMI, waist circumference, and trunk fat were considered together, only trunk fat remained independently associated with increased ALT.

Conclusions—Trunk fat is a major body composition determinant of increased ALT, supporting the hypothesis that liver injury can be induced by metabolically active intra-abdominal fat.

Keywords

alanine aminotransferase; body composition; dual-energy x-ray absorptiometry; National Health and Nutrition Examination Survey

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INTRODUCTION

Obesity is an important risk factor for liver injury. A central fat distribution may be more important than total adipose mass.^{1, 2} In the general population, liver injury has been associated with anthropometric measures, such as body mass index (BMI) and waist circumference.³ Although this relationship is presumed to be determined by fat mass, a limitation of BMI and other anthropometric measures is that they reflect both fat and lean mass. The relationship of liver injury with body mass components using actual measures of body composition such as dual X-ray absorptiometry (DXA) has not been evaluated in a population-based study. We examined the individual and relative contributions of body composition, measured with DXA, to elevated serum alanine aminotransferase (ALT) among US adults without evidence of chronic viral hepatitis in a national population-based sample.

METHODS

The National Health and Nutrition Examination Survey (NHANES) is conducted in the United States by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and since 1999 has been a continuous annual survey.⁴ It consists of cross-sectional interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample representative of the civilian, noninstitutionalized population with oversampling of persons aged 60 years and older, African-Americans, and Hispanics. The survey was approved by the CDC Institutional Review Board and all participants provided written informed consent to participate. The current analysis utilized data collected from 1999 through 2004, the 6 years of performance of DXA body composition measurements.

Refrigerated serum samples were shipped weekly to testing labs. From 1999-2001 serum ALT activity was assayed by a Hitachi model 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN) at the Coulston Foundation, Alamogordo, NM and from 2002-2004 by a Beckman Synchron LX20 (Beckman Coulter Inc., Fullerton, CA) at Collaborative Laboratory Services, L.L.C., Ottumwa, IA.⁵⁻⁸ ALT activity distributions did not differ between the Coulston Foundation Laboratory and Collaborative Laboratory Services.⁹ ALT was considered abnormal if higher than the 95th percentile among US adults not at high risk for liver injury (negative for viral hepatitis B and C, alcohol consumption ≤ 2 drinks per day, BMI $< 25 \text{ kg/m}^2$, waist circumference $\leq 102 \text{ cm}$ among men and $\leq 88 \text{ cm}$ among women, no doctor-diagnosed diabetes and hemoglobin A_{1C} $\leq 6.7\%$ [95th percentile among all US adults]). These cut-offs were 44 IU/L for men and 31 IU/L for women.

Arm, leg, and trunk fat mass and lean soft-tissue mass were measured by DXA by using a Hologic QDR 4500A fan-beam densitometer (Hologic Inc., Bedford, MA); Hologic Discovery software version 12.1 was used for analysis of the scans.¹⁰⁻¹² The NHANES 1999-2004 Multiple Imputation Data Files, as released by the National Center for Health Statistics, were used for this analysis (see statistical analysis section for additional information).⁴ Height was measured using a stadiometer.¹⁴ Arm and leg fat summed to extremity fat mass, while arm and leg fat-free mass minus bone mineral content summed to extremity lean tissue mass. We calculated four body composition indices by dividing trunk and extremity fat masses and trunk and extremity lean soft tissue masses (kg) by height (m) squared. These index measures accounted for variation in fat and lean mass due to variation in height and are analogous to BMI (kg/m^2).¹² Body composition indices and waist circumference (cm) were categorized as quintiles because they were not normally distributed and because extreme values could exert undue influence if coded as continuous variables.

Factors known or thought to be related to elevated ALT or body composition were included as covariates in multivariate analyses: age (years), sex, ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other), cigarette smoking (never, former, < 1 pack/day, $\geq$ 1 pack/day), alcohol consumption (drinks/day; 0, <1, 1–2, >2), glucose status (abnormal if doctor-diagnosed diabetes or elevated hemoglobin A_{1C}), and serum total cholesterol concentration (mg/dL). Among a subgroup of participants who attended a morning examination after an overnight fast, concentrations of plasma glucose (mg/dL), serum C-peptide (nmol/L), and serum triglycerides (mg/dL) were determined.³

Of 20,228 sampled persons age 20 years and older, 14,213 (70%) were examined. We excluded participants positive for serum hepatitis B surface antigen or positive or indeterminate for hepatitis C antibody (n=379), missing viral hepatitis serology (n=867), pregnant women (n=711), highly variable imputed or missing DXA data (n=244), missing height (n=115) or missing serum ALT activity (n=76). The analysis sample, therefore, consisted of 11,821 participants. Of the 11,821 participants, 2,579 had some or all imputed DXA data. Measures of insulin resistance have been shown to be strongly related to elevated ALT,³ but were only available for a subgroup of participants. Therefore, a secondary analysis of 5,331 participants randomly assigned to be examined in the morning after an overnight fast excluded 907 who missed the morning examination or who fasted <8 or >24 hours.

Statistical analysis

Missing DXA data, due to no scan or an invalid scan, were non-random (that is, more frequent with greater age, BMI, weight, and height) which could lead to biased population estimates if simply excluded from analyses. Therefore, missing DXA data were imputed by NCHS using multiple-imputation methodology.^{11–13} Five versions of imputed values were generated randomly and independently resulting in five complete data sets of measured and imputed values. Imputation introduces extra variability because the imputed values are plausible replacements, but not the true values. Therefore, each of the five data sets was analyzed separately and the results combined. The variability across the five analyses reflects the additional variability due to imputation. For the current analysis, multiply imputed DXA data were analyzed using the built-in option (MI_COUNT=x in the PROC statement where x is the number of datasets) found in SUDAAN software (SUDAAN User's Manual, Release 10.0, 2008; Research Triangle Institute, Research Triangle Park, NC).

Because of sex differences in ALT levels and body composition, separate analyses were conducted for men and women. Mean body composition indices were compared by categories of participant characteristics, and in persons with and without abnormal ALT activity, using a t-test. To further examine the relation of elevated ALT with body composition indices, the prevalence of elevated ALT was compared among body composition index quintiles. Multivariate logistic regression analysis (SUDAAN, PROC RLOGIST, SUDAAN User's Manual, Release 10.0, 2008; Research Triangle Institute, Research Triangle Park, NC) was then used to calculate odds ratio estimates and 95% confidence intervals for elevated ALT, while controlling for the effects of other factors related to abnormal ALT activity. Odds ratios were computed for each body composition index quintile relative to the lowest quintile by categorizing these indices as indicator variables. The trend in odds ratios across quintiles of body composition indices was tested by treating these indices as ordinal variables of five levels. Interaction between body composition indices was tested by categorizing indices as tertiles, in order to have adequate cell sizes, and including interaction terms in models.

Because body composition measures are correlated, analyses were conducted using both standard multivariate logistic regression and the residual method, which removes the potentially distorting effect of collinearity of two highly correlated variables, such as body composition measures.¹⁸ In the residual method, models contained one body composition

index and the residual of a second body composition index (the variable of interest) that was regressed on the first in an initial step. Body composition indices were treated as ordinal variables of five levels for analyses using the residual method.

An analysis was also conducted of the relationship of elevated ALT with BMI and waist circumference to evaluate whether DXA measures were better predictors of abnormal ALT than were BMI and waist circumference. Multivariate analyses were conducted among participants examined in the morning after an overnight fast to adjust for fasting plasma glucose and serum C-peptide and triglyceride concentrations. In addition, an analysis was performed to examine whether DXA measures explained sex and race-ethnicity differences in prevalence of elevated ALT. Body composition indices were treated as continuous variables for this analysis.

Multivariate analyses excluded persons with missing values for any factor included in the model. A p-value of <0.05 indicated statistical significance. All analyses utilized sample weights that accounted for unequal selection probabilities and nonresponse. All variance calculations took into consideration the design effects of the survey using Taylor series linearization.¹⁹ Analyses were conducted using SUDAAN software (SUDAAN User's Manual, Release 10.0, 2008; Research Triangle Institute, Research Triangle Park, NC). When using the sample weights, this software enables the strata and primary sampling unit pairings from the sample design to also be used in estimating variances and testing for statistical significance. As advised by the NHANES sponsor,²⁰ such consideration of the complex sample design is necessary to accurately determine the precision and statistical significance of any statistic.

RESULTS

Mean (SD) body composition indices for the 5,903 men and 5,918 women included in the analyses are shown in Tables 1a and 1b (first row); ranges and quintile cut-points are shown in Tables 3a and 3b (footnote). Fat mass tended to increase in middle age, while lean mass tended to decrease in older age (Tables 1a and 1b). Among men, non-Hispanic blacks had lower fat and lean trunk mass and higher extremity lean mass than either non-Hispanic whites or Mexican-Americans (Table 1a). Among women, blacks had higher levels of all body composition measures than whites, while Mexican-Americans had higher levels of fat and lean trunk mass than whites (Table 1b). All body composition measures were higher with elevated glucose concentration and lower with greater alcohol consumption among both men and women (Tables 1a and 1b). Former smokers had higher fat and lean trunk mass, among both men and women, while current smokers tended to have lower levels of all body composition measures (Tables 1a and 1b).

Relationship of ALT to body measurements

The prevalence ($\pm$ SE) of elevated ALT was 11.1% ($\pm$ 0.56%) among men and 10.1% ($\pm$ 0.36%) among women. Means of all body composition measures were higher with elevated ALT compared with normal ALT among both men and women ($p < 0.001$ for all comparisons) (Table 2). Likewise, unadjusted prevalence of elevated ALT increased across quintiles of all body measures among men and women (Tables 3a and 3b). The association of elevated ALT with individual body measures of BMI, waist circumference and the four compositions was evaluated in logistic regression analyses (Table 4). An increased odds of higher ALT was seen with increasing quintiles of all body measures among men and women in both unadjusted models (p -value for trend < 0.001 for all comparisons) and after adjusting for alcohol consumption and other liver injury risk factors (p -value for trend < 0.001 for all comparisons). Of the four DXA measures, the relationship was strongest with trunk fat, especially among men. The higher risk of elevated ALT with greater trunk fat among men in the multivariate-

adjusted analysis (OR=11.6 comparing highest to lowest quintile) than unadjusted analysis (OR=7.1) was primarily the result of adjusting for age.

Analysis was performed for the combined effect of body composition measures on elevated ALT. In multivariate-adjusted models including trunk fat and one of the other three body composition indices, higher trunk fat remained strongly associated with elevated ALT ($p \leq 0.001$ for all comparisons) among both men and women (data not shown). Among women, an independent inverse relationship emerged with extremity fat. The odds ratios (OR) (95% confidence intervals (CI)) comparing the second through fifth quintiles, respectively, relative to the first quintile were 0.51 (0.34-0.78), 0.56 (0.38-0.83), 0.45 (0.29-0.69), and 0.27 (0.16-0.47) (p -value for trend < 0.001). Among men, an inverse relationship with extremity fat also appeared after adjustment for trunk fat, but did not reach statistical significance. The ORs (95% CIs) comparing the upper quintiles relative to the lowest quintile among men were 0.79 (0.43-1.5), 0.58 (0.33-1.0), 0.59 (0.30-1.2), and 0.55 (0.27-1.1) (p -value for trend=0.13). Trunk lean mass was of borderline statistical significance among men ($p=0.050$) and women ($p=0.071$). Extremity lean mass was not independently related to ALT among either men or women ($p > 0.10$).

When all four body composition indices were included in multivariate-adjusted models, higher trunk fat remained independently associated with elevated ALT among both men (Figure 1a) and women (Figure 1b). Compared with the lowest quintile, the odds ratio for elevated ALT among men in the highest quintile of trunk fat was 13.8 (95% CI 5.4-35.3), and among women it was 7.8 (95% CI 3.9-15.8). Among women, extremity fat was inversely associated with elevated ALT with adjustment for trunk fat (Figure 1b). Thus, compared with the lowest quintile, women in the highest quintile were only a quarter as likely to have an elevated ALT (OR (95% CI) =0.24 (0.14-0.42)). However, this relationship was found only among women with the highest degree of trunk fat (Figure 2) (test for interaction $p=0.043$). Among men, an inverse relationship with extremity fat was also found, but was not statistically significant (OR (95% CI) comparing the highest to lowest quintile =0.52 (0.26-1.1)) (Figure 1a). Trunk lean and extremity lean mass were not independently related to ALT among either men or women. To address the possible effect on ALT measurement of impaired renal function, an additional analysis excluded 1,220 participants with moderately or severely decreased glomerular filtration rate (GFR) (defined as an estimated GFR of < 60 mL/min/1.73 m²).²¹ There was little effect on the relationship of elevated ALT with body composition indices among either men or women (data not shown). To evaluate the possible confounding effect of potentially hepatotoxic medications used more often in the overweight and obese, an additional analysis was conducted among 5,120 participants not taking prescriptions medications. Elevated ALT remained strongly associated with higher trunk fat among both men and women and inversely related to higher extremity fat among women (data not shown).

Having established that elevated ALT was most strongly associated with trunk fat, we considered its effect on the association of BMI and waist circumference with elevated ALT. When trunk fat, BMI, and waist circumference were included together in multivariate-adjusted models, higher trunk fat remained independently associated with elevated ALT among both men ($p=0.002$) (Figure 1c) and women ($p=0.011$) (Figure 1d), but BMI and waist circumference were not (p -value for trend > 0.10 for all comparisons). However, women in the highest three quintiles of waist circumference were more likely to have ALT elevation than women in the lower two quintiles (OR=1.2, 95% CI 0.95-1.4).

Because body composition measures are strongly correlated, relationships were further evaluated in analyses containing trunk fat and the residual of one of the other measures regressed on trunk fat (Table 5). This enabled us to examine the information contained in each of the other 3 body composition indices that was not accounted for by trunk fat. As with analyses

using standard multivariate logistic regression, trunk fat remained the dominant body composition measure among both men and women. The residual of extremity fat was inversely related to elevated ALT among women ($p=0.001$) and men ($p=0.002$). The residuals of BMI and waist circumference were not independently related to elevated ALT among men or women.

A secondary analysis was conducted among a random subgroup of 5,331 participants examined in the morning after an overnight fast, adjusting for fasting plasma glucose and serum triglyceride and C-peptide concentrations, in addition to the factors adjusted for in the main analysis. Among men in the AM fasting sample, the association of elevated ALT with trunk fat was reduced modestly with adjustment for these other factors. The OR (95% CI) comparing the highest relative to lowest trunk fat quintile was 6.1 (2.8-13.7) (Supplementary Table 1) as compared with 11.6 (7.9-16.9) in the main analysis (Table 4). Among women the association of abnormal ALT with trunk fat was attenuated, primarily by C-peptide concentration. The OR (95% CI) comparing the highest relative to lowest trunk fat index quintile was 2.6 (1.0-6.4) (Supplementary Table 2) as compared with 4.6 (3.0-7.1) in the main analysis without adjustment for C-peptide (Table 4).

Finally, analyses were performed to examine whether trunk fat explained sex and race-ethnicity differences in prevalence of elevated ALT. For the analysis of sex, the same cut-point for elevated ALT was used for both men and women (>38 IU/L, defined similarly to the cut-points for men and women individually by using the 95th percentile among US adults not at high risk for liver injury). In multivariate analysis using the same cut-point for elevated ALT for both men and women, the odds ratio for ALT elevation was 3.1 (95% CI=2.7–3.6) for men relative to women, which increased to 4.5 (95% CI=3.7–5.4) with adjustment for trunk fat (Supplementary Table 3). Compared with non-Hispanic white men, the odds ratio for elevated ALT was 0.66 (95% CI=0.47–0.92) for non-Hispanic black men and 2.0 (95% CI=1.5–2.6) for Mexican-American men. Adjustment for trunk fat attenuated the lower risk among black men (OR=0.75, 95% CI=0.53–1.1), but not the higher risk among Mexican-American men (Supplementary Table 3). Compared with non-Hispanic white women, the odds ratio for elevated ALT was 0.52 (95% CI=0.38–0.72) for non-Hispanic black women and 2.0 (95% CI=1.5–2.6) for Mexican-American women. Adjustment for trunk fat had little effect on these relationships (Supplementary Table 3).

DISCUSSION

The main finding of this large, national, population-based study was a strong association of higher trunk fat mass index (trunk fat mass/height squared) with abnormal ALT activity. This relationship was found among both men and women and was independent of extremity fat, trunk lean, and extremity lean mass, BMI, waist circumference and of other liver injury risk factors. A measure of insulin resistance attenuated, but did not eliminate the relationship among women. In an analysis of an earlier NHANES, an elevated ALT was associated with a central fat distribution as measured by anthropometric indicators such as waist circumference or waist-to-hip circumference ratio (WHR).³ WHR is considered to be a measure of upper versus lower body adiposity. However, circumferences are influenced by both fat and lean mass and a higher WHR may reflect both increased upper body fat and decreased lower body fat. DXA provides a more direct and accurate measurement of total and regional (i.e. trunk, arm, leg) fat and lean body mass. In clinical and epidemiologic studies, hepatic steatosis has been associated with abdominal adiposity^{22–34} with few exceptions.^{35, 36} This relationship was found among both men and women and obese and non-obese persons. In most studies using imaging methods to measure abdominal fat, intraabdominal fat but not subcutaneous abdominal fat was associated with liver fat.^{22, 24, 25, 28, 30–34} The relationship of liver injury with greater trunk fat is therefore likely attributable to the visceral adipose component. It has been hypothesized that visceral fat

releases potentially hepatotoxic fatty acids and adipokines into the portal vein where they exert a first-pass effect on the liver.^{22, 37} Visceral adipose tissue lipolysis is also less sensitive to insulin suppression than other fat depots.³⁸

Despite the strength of the relationship of trunk fat with abnormal ALT, it did not explain the higher prevalence of elevated ALT among men compared with women. In fact, because women tend to have higher trunk fat and lower ALT than men the relationship of ALT with male sex was strengthened by this adjustment. Trunk fat partially explained the lower prevalence of abnormal ALT among non-Hispanic black men compared with non-Hispanic white men, but not the higher prevalence among Mexican-American men or any race-ethnic differences among women.

An unexpected finding was a relationship of decreased extremity fat with elevated ALT after adjusting for trunk fat. Extremity or leg fat mass measured by DXA has been shown to be inversely associated with metabolic risk factors independent of trunk fat.³⁹⁻⁴⁶ Higher peripheral fat has also been reported to be favorably related to coronary atherosclerosis^{42, 47} and peripheral arterial stiffness.^{48, 49} Nonalcoholic fatty liver is associated with dyslipidemia, glucose intolerance, and insulin resistance and has been considered to be the liver manifestation of the metabolic syndrome.⁵⁰⁻⁵² However, little is known about the relationship of peripheral fat mass with liver injury. In a clinical study of French patients referred for overweight/obesity, ALT was independently related positively to trunk fat mass and inversely to leg fat mass among men and women.⁵³ Among Chinese patients, low femoral subcutaneous fat was associated with ultrasound-diagnosed fatty liver independent of visceral fat and abdominal subcutaneous fat among women, but not men.⁵⁴ The metabolism of adipose tissue differs based on its central or peripheral location. Lipoprotein lipase activity is higher in leg fat compared with trunk fat resulting in decreased fatty acid turnover.^{55, 56} Uptake and storage of free fatty acids by femoral adipose tissue could lead to protection of other organs such as the liver from exposure to fatty acids and ectopic fat deposition.⁵³

As previously reported, limitations of using NHANES to study liver injury are reliance on serum measures to estimate liver injury. Liver biopsies cannot be conducted on the general population, and imaging was not performed. Therefore, a single serum liver enzyme activity was relied upon as a marker for liver injury.^{3, 57, 58} Inevitably, participants were included in the elevated ALT group who would not have been had repeat ALT measurements been available. Several limitations of DXA should be appreciated. Trunk fat measured by DXA does not differentiate between subcutaneous and visceral adipose tissue and parenchymal fat, including that in the liver. Thus abdominal fat measurements by DXA are not necessarily comparable to adipose tissue measurements by CT or MRI. In addition, soft-tissue composition can only be determined on pixels free of bone. In the arm and leg, the percentage of bone-free pixels is lower than in the trunk, which may have resulted in less accurate measures of extremity soft tissue composition. For a number of larger and older participants, multiple imputation methods were used to adjust for their missing DXA data. An additional limitation of this study is its cross-sectional design. The current results do not necessarily indicate that reduction of trunk fat will reduce liver injury. Factors in common, such as insulin resistance, could be more significant. These limitations are balanced by the benefits of a large, national, population-based sample, particularly the avoidance of ascertainment bias that occurs in clinical studies of selected patients, and the ability to generalize the results to the U.S. population. Despite the limitations mentioned above, a major strength of the study was the use of DXA, a relatively accurate and precise method to estimate body fat and lean soft tissue mass components.

These results in the U.S. population indicate that trunk fat is the major body composition determinant of elevated ALT activity. They support the hypothesis that liver injury can be induced by metabolically active intra-abdominal fat.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DXA	dual-energy X-ray absorptiometry
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
SE	standard error
WHR	waist-to-hip circumference ratio

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Figure 1a.
Multivariate-adjusted OR for elevated ALT comparing upper relative to lowest body composition index quintile and adjusting for all 3 other measures among men

Figure 1b.

Multivariate-adjusted OR for elevated ALT comparing upper relative to lowest body composition index quintile and adjusting for all 3 other measures among women

Figure 1c.

Multivariate-adjusted OR for elevated ALT comparing upper relative to lowest quintile of trunk fat, BMI, and waist circumference and adjusting for the other 2 measures among men

Figure 1d.

Multivariate-adjusted OR for elevated ALT comparing upper relative to lowest quintile of trunk fat, BMI, and waist circumference and adjusting for the other 2 measures among women

Figure 2.
Prevalence of elevated ALT by trunk fat and extremity fat tertiles among women

Table 1a
Mean (SD) body measure indices (kg/m²) and waist circumference (cm) by characteristics among men (n=5,903)

Characteristic	Fat		Lean		Waist circumference
	Trunk	Extremity	Trunk	Extremity	
All	4.3 (1.9)	3.5 (1.4)	9.5 (1.4)	8.6 (1.3)	99.6 (14.7)
Age (years)					
20-39	3.7 (1.9)	3.4 (1.5)	9.3 (1.3)	8.7 (1.4)	94.9 (15.0)
40-59	4.6 (1.9)*	3.6 (1.3)*	9.7 (1.4)*	8.7 (1.3)	102.2 (13.8)*
60+	4.9 (1.8)*†	3.6 (1.2)*	9.5 (1.3)*†	8.0 (1.2)*†	104.5 (12.8)*†
Race-ethnicity					
NHW	4.4 (1.9)	3.6 (1.3)	9.5 (1.4)	8.5 (1.3)	101.0 (14.4)
NHB	3.7 (2.1)*	3.5 (1.7)	9.3 (1.5)*	9.3 (1.6)*	95.8 (16.6)*
Mex-Am	4.3 (1.7)†	3.4 (1.2)*	9.5 (1.2)†	8.5 (1.1)†	97.0 (12.7)*
Other	4.0 (1.7)*†‡	3.2 (1.2)*†	9.2 (1.4)*†	8.4 (1.4)†	95.0 (14.2)*
Glucose status					
Normal	4.2 (1.8)	3.5 (1.3)	9.4 (1.3)	8.6 (1.3)	98.7 (14.2)
Abnormal§	5.8 (2.3)*	4.1 (1.6)*	10.4 (1.6)*	8.8 (1.5)*	109.8 (15.7)*
Smoking					
Never	4.3 (1.9)	3.6 (1.4)	9.5 (1.4)	8.8 (1.4)	99.3 (14.8)
Former	4.7 (1.9)*	3.7 (1.3)	9.7 (1.3)*	8.6 (1.3)*	103.2 (13.8)*
<1 pack/day	3.8 (1.9)*†	3.2 (1.4)*†	9.3 (1.4)*†	8.4 (1.3)*	95.4 (14.7)*†
≥1 pack/day	3.8 (1.8)*†	3.2 (1.2)*†	9.4 (1.3)†	8.2 (1.2)*†	97.2 (14.3)*†‡
Alcohol intake					
0	4.8 (2.2)	3.8 (1.6)	9.7 (1.6)	8.6 (1.5)	103.5 (16.2)
<1	4.2 (1.9)*	3.5 (1.3)*	9.4 (1.3)*	8.6 (1.3)	98.8 (14.7)*
1-2	3.9 (1.5)*†	3.2 (1.0)*†	9.3 (1.1)*	8.5 (1.1)*†	97.4 (11.9)*†
>2	4.0 (1.8)*	3.3 (1.2)*†	9.4 (1.3)*	8.4 (1.2)*†	98.5 (13.5)*

NHW = non-Hispanic white, NHB = non-Hispanic black, Mex-Am = Mexican-American

* p<0.05 compared with 1st listed category.

[†] p<0.05 compared with 2nd listed category.

[‡] p<0.05 compared with 3rd listed category.

[§] Doctor-diagnosed diabetes or hemoglobin A1C > 6.8% (95th percentile).

Table 1b
Mean (SD) body measure indices (kg/m²) and waist circumference (cm) by characteristics among women (n=5,918)

Characteristic	Fat		Lean		Waist circumference
	Trunk	Extremity	Trunk	Extremity	
All	5.6 (2.6)	5.8 (2.2)	8.1 (1.3)	6.7 (1.3)	93.1 (15.6)
Age (years)					
20-39	5.0 (2.7)	5.5 (2.2)	8.0 (1.2)	6.9 (1.3)	89.3 (15.8)
40-59	5.9 (2.7)*	6.0 (2.3)*	8.3 (1.4)*	6.8 (1.4)	94.7 (15.9)*
60+	5.9 (2.1)*	5.9 (2.0)*	8.0 (1.1) [†]	6.4 (1.2) ^{**†}	96.5 (13.8) ^{**†}
Race-ethnicity					
NHW	5.5 (2.6)	5.7 (2.1)	8.1 (1.3)	6.6 (1.2)	92.6 (15.6)
NHB	6.1 (2.8)*	6.8 (2.6)*	8.4 (1.4)*	7.9 (1.5)*	98.6 (16.6)*
Mex-Am	6.1 (2.4)*	5.7 (1.9) [†]	8.4 (1.3)*	6.7 (1.2) ^{**†}	93.9 (14.5) [†]
Other	5.4 (2.3) ^{††}	5.4 (1.9) ^{**††}	7.9 (1.2) ^{††}	6.6 (1.2) [†]	90.4 (14.3) ^{††}
Glucose status					
Normal	5.4 (2.5)	5.7 (2.2)	8.0 (1.2)	6.7 (1.3)	92.1 (15.1)
Abnormal [§]	7.5 (2.8)*	6.6 (2.5)*	9.1 (1.4)*	7.3 (1.6)*	106.5 (16.0)*
Smoking					
Never	5.5 (2.6)	5.8 (2.2)	8.0 (1.3)	6.8 (1.3)	92.6 (15.4)
Former	5.9 (2.6)*	6.0 (2.2)	8.2 (1.3)*	6.7 (1.3)	95.2 (15.9)*
<1 pack/day	5.3 (2.7) [†]	5.5 (2.3) ^{**†}	8.1 (1.3)	6.8 (1.4)	92.0 (16.2) [†]
≥1 pack/day	5.4 (2.5) [†]	5.4 (2.0) ^{**†}	8.2 (1.3)*	6.6 (1.3)	93.2 (15.4)
Alcohol intake					
0	6.1 (2.7)	6.1 (2.3)	8.3 (1.4)	6.8 (1.4)	96.5 (16.2)
<1	5.3 (2.5)*	5.7 (2.2)*	8.0 (1.2)*	6.7 (1.3)*	91.5 (15.4)*
1-2	5.0 (2.2) ^{**†}	5.1 (1.7) ^{**†}	7.8 (1.0) ^{**†}	6.4 (1.1) ^{**†}	91.1 (13.6)*
>2	4.6 (1.9) ^{**†}	4.8 (1.6) ^{**†}	7.6 (1.0) ^{**†}	6.4 (1.1) ^{**†}	88.7 (12.9)*

NHW = non-Hispanic white, NHB = non-Hispanic black, Mex-Am = Mexican-American

* p<0.05 compared with 1st listed category.

[†] p<0.05 compared with 2nd listed category.

[‡] p<0.05 compared with 3rd listed category.

[§] Doctor-diagnosed diabetes or hemoglobin A1C > 6.8% (95th percentile).

Table 2

Mean (SD) body measure indices (kg/m²) and waist circumference (cm) by serum alanine aminotransferase (ALT) status* among men and women

Body measure	Men				Women			
	ALT (IU/L)		ALT (IU/L)		ALT (IU/L)		ALT (IU/L)	
	<44 (n=5,286)	>44 (n=617)	Difference	95% CI of difference	≤31 (n=5,281)	>31 (n=637)	Difference	95% CI of difference
Trunk fat	4.2 (1.9)	5.3 (1.9)	1.1	0.93 - 1.3	5.4 (2.5)	6.7 (2.8)	1.2	0.95 - 1.5
Extremity fat	3.4 (1.3)	4.0 (1.4)	0.60	0.50 - 0.70	5.7 (2.2)	6.2 (2.3)	0.49	0.23 - 0.75
Trunk lean	9.4 (1.3)	10.1 (1.4)	0.74	0.60 - 0.88	8.0 (1.2)	8.6 (1.4)	0.58	0.45 - 0.72
Extremity lean	8.5 (1.3)	9.2 (1.4)	0.66	0.53 - 0.79	6.7 (1.3)	7.1 (1.3)	0.38	0.26 - 0.51
BMI	27.6 (5.3)	30.8 (5.7)	3.2	2.7 - 3.6	27.9 (6.9)	30.7 (7.3)	2.8	2.0 - 3.5
Waist circumference	98.8 (14.4)	106.3 (14.8)	7.5	6.1 - 8.9	92.4 (15.5)	99.2 (16.0)	6.8	5.3 - 8.3

* p<0.001 for all comparisons.

Table 3a

Prevalence (%; SE) of elevated serum alanine aminotransferase (ALT)* by body measure quintile† among men (n=5,903)

Body measure	Quintile‡				
	1st	2nd	3rd	4th	5th
Trunk fat	3.5 (0.59)	6.9 (0.75)	12.3 (1.3)	12.8 (1.2)	20.4 (1.7)
Extremity fat	5.1 (0.70)	8.9 (0.93)	9.6 (1.1)	13.6 (1.3)	18.5 (1.3)
Trunk lean	5.1 (0.70)	7.4 (0.96)	9.9 (0.88)	12.9 (1.4)	20.4 (1.6)
Extremity lean	5.3 (0.69)	8.8 (0.87)	8.5 (0.96)	13.5 (1.4)	19.6 (1.6)
BMI	3.9 (0.54)	6.6 (0.93)	10.4 (0.98)	14.7 (1.5)	20.2 (1.4)
Waist circumference	3.9 (0.57)	9.2 (1.0)	10.1 (1.1)	14.1 (1.3)	18.4 (1.5)

* 44 IU/L.

† p<0.001 for all comparisons.

‡ Quintile definitions for body measure indices (kg/m²) and waist circumference (cm), respectively, were as follows: for trunk fat, 0.47-2.6, 2.6-4.5, 4.5-5.7, and 5.7-16.1; for extremity fat, 0.85-2.5, 2.5-3.0, 3.0-3.6, 3.6-4.4, and 4.4-15.3; for trunk lean, 4.8-8.4, 8.4-9.1, 9.1-9.6, 9.6-10.5, and 10.5-18.8; for extremity lean, 3.9-7.5, 7.5-8.2, 8.2-8.8, 8.8-9.5, and 9.5-18.2; for BMI, 16.0-23.7, 23.7-26.1, 26.1-28.5, 28.5-31.7, and 31.7-65.0; and for waist circumference, 62.4-87.5, 87.5-95.1, 95.1-101.8, 101.8-110.8, and 110.8-173.4.

Table 3b
Prevalence (%; SE) of elevated serum alanine aminotransferase (ALT)* by body measure quintile† by body measure quintile‡ among women (n=5,918)

Body measure	Quintile‡				
	1st	2nd	3rd	4th	5th
Trunk fat	4.3 (0.75)	7.3 (0.79)	9.4 (0.90)	12.7 (1.2)	16.7 (1.1)
Extremity fat	7.7 (0.72)	7.0 (0.95)	11.0 (0.94)	12.3 (0.93)	12.3 (1.1)
Trunk lean	5.2 (0.80)	7.3 (1.0)	9.5 (1.2)	12.0 (1.2)	16.5 (1.2)
Extremity lean	6.0 (0.78)	8.4 (0.88)	10.2 (1.1)	11.4 (1.1)	14.4 (1.2)
BMI	5.4 (0.74)	6.9 (0.84)	10.2 (0.85)	12.1 (1.0)	15.9 (1.0)
Waist circumference	4.1 (0.75)	7.2 (0.89)	12.2 (1.2)	10.8 (0.99)	15.7 (1.0)

* 31 IU/L.

† p<0.001 for all comparisons.

‡ Quintile definitions for body measure indices (kg/m²) and waist circumference (cm), respectively, were as follows: for trunk fat, 0.67-<3.3, 3.3-<4.6, 4.6-<5.9, 5.9-<7.5, and 7.5-18.2; for extremity fat, 0.79-<4.0, 4.0-<4.9, 4.9-<5.9, 5.9-<7.3, and 7.3-20.6; for trunk lean, 3.9-<7.0, 7.0-<7.6, 7.6-<8.2, 8.2-<9.0, and 9.0-14.8; for extremity lean, 3.5-<5.7, 5.7-<6.2, 6.2-<6.8, 6.8-<7.7, and 7.7-15.4; for BMI, 12.0-<22.4, 22.4-<25.3, 25.3-<28.6, 28.6-<33.4, and 33.4-66.4; and for waist circumference, 58.5-<79.1, 79.1-<87.4, 87.4-<95.7, 95.7-<105.8, and 105.8-157.7.

The relationship* of elevated serum alanine aminotransferase (ALT)[†] with body measure indices (kg/m²) and waist circumference (cm) among men and women

Men				Women					
Body measure quintile	Unadjusted (n=5,903)		Multivariate-adjusted [‡] (n=5,900)		Body measure quintile	Unadjusted (n=5,918)		Multivariate-adjusted [‡] (n=5,496)	
	OR [§]	95% CI	OR [§]	95% CI		OR [§]	95% CI	OR [§]	95% CI
Trunk fat									
< 2.6	1.0		1.0		< 3.3		1.0		
2.6 - < 3.6	2.1	1.4 - 3.1	2.3	1.5 - 3.6	3.3 - < 4.6		1.8	1.2 - 2.7	1.9
3.6 - < 4.5	3.9	2.6 - 5.9	4.8	3.2 - 7.2	4.6 - < 5.9		2.3	1.5 - 3.6	2.5
4.5 - < 5.7	4.1	2.5 - 6.6	5.6	3.5 - 9.2	5.9 - < 7.5		3.3	2.0 - 5.3	3.5
≥ 5.7	7.1	4.9 - 10.3	11.6	7.9 - 16.9	≥ 7.5		4.5	3.0 - 6.7	4.6
Extremity fat									
< 2.5	1.0		1.0		< 4.0		1.0		
2.5 - < 3.0	1.8	1.2 - 2.7	1.8	1.2 - 2.8	4.0 - < 4.9		0.90	0.63 - 1.3	0.89
3.0 - < 3.6	2.0	1.4 - 2.8	2.1	1.4 - 3.0	4.9 - < 5.9		1.5	1.2 - 1.9	1.5
3.6 - < 4.4	2.9	1.9 - 4.4	3.0	1.9 - 4.8	5.9 - < 7.3		1.7	1.3 - 2.2	1.7
≥ 4.4	4.2	3.1 - 5.6	5.1	3.6 - 7.3	≥ 7.3		1.7	1.2 - 2.3	1.7
Trunk lean									
< 8.4	1.0		1.0		< 7.0		1.0		
8.4 - < 9.1	1.5	0.98 - 2.3	1.6	1.0 - 2.5	7.0 - < 7.6		1.4	0.87 - 2.4	1.5
9.1 - < 9.6	2.1	1.4 - 3.0	2.2	1.4 - 3.2	7.6 - < 8.2		1.9	1.2 - 3.1	2.0
9.6 - < 10.5	2.8	1.9 - 4.0	2.9	2.0 - 4.3	8.2 - < 9.0		2.5	1.6 - 3.8	2.6
≥ 10.5	4.8	3.4 - 6.8	5.7	4.0 - 8.2	≥ 9.0		3.6	2.4 - 5.4	3.6
Extremity lean									
< 7.5	1.0		1.0		< 5.7		1.0		
7.5 - < 8.2	1.7	1.2 - 2.5	1.5	1.0 - 2.2	5.7 - < 6.2		1.5	0.96 - 2.2	1.5
8.2 - < 8.8	1.7	1.2 - 2.4	1.4	0.94 - 2.0	6.2 - < 6.8		1.8	1.2 - 2.8	2.0
8.8 - < 9.5	2.8	2.0 - 4.0	2.4	1.7 - 3.4	6.8 - < 7.7		2.0	1.4 - 3.0	2.3

Body measure quintile	Men			Women		
	Unadjusted (n=5,903)		Body measure quintile	Multivariate- adjusted [‡] (n=5,590)		Multivariate- adjusted [‡] (n=5,496)
	OR [§]	95% CI		OR [§]	95% CI	
≥ 9.5	4.3	3.1 - 6.1	≥ 7.7	2.7	1.9 - 3.7	2.2 - 4.7
BMI						
< 23.7	1.0		< 22.4	1.0		
23.7 - < 26.1	1.8	1.1 - 2.8	22.4 - < 25.3	1.3	0.88 - 2.0	0.87 - 2.0
26.1 - < 28.5	2.8	1.9 - 4.3	25.3 - < 28.6	2.0	1.4 - 2.9	1.4 - 3.0
28.5 - < 31.7	4.2	2.9 - 6.3	28.6 - < 33.4	2.4	1.6 - 3.6	1.7 - 3.8
≥ 31.7	6.2	4.4 - 8.9	≥ 33.4	3.3	2.3 - 4.8	2.3 - 4.9
Waist circumference						
< 87.5	1.0		< 79.1	1.0		
87.5 - < 95.1	2.5	1.6 - 3.9	79.1 - < 87.4	1.8	1.1 - 2.9	1.2 - 3.2
95.1 - < 101.8	2.8	1.8 - 4.3	87.4 - < 95.7	3.2	2.0 - 5.2	2.2 - 6.0
101.8 - < 110.8	4.1	2.9 - 5.9	95.7 - < 105.8	2.8	1.9 - 4.3	2.0 - 5.0
≥ 110.8	5.6	3.8 - 8.2	≥ 105.8	4.3	2.8 - 6.6	3.1 - 7.8

* p-value for trend <0.001 for all body composition measures in both unadjusted and multivariate-adjusted analyses.

[†] >44 IU/L for men or >31 IU/L for women.

[‡] Adjusted for ethnicity, age (6 categories, ordinal), glucose status (doctor-diagnosed diabetes, elevated hemoglobin A1C), serum total cholesterol, cigarette smoking, and alcohol consumption.

[§] Calculated from logistic regression analysis.

Table 5

The relationship of elevated serum alanine aminotransferase (ALT)^{*} with trunk fat mass index and residuals of body measure indices (kg/m²) and waist circumference (cm) regressed on trunk fat among men and women in multivariate-adjusted[‡] analysis using the residual method

	Men (n=5,590)			Women (n=5,496)		
	OR [‡]	95% CI	p-value	OR [‡]	95% CI	p-value
Trunk fat [§]	1.7	1.6–1.9	<0.001	1.4	1.3–1.5	<0.001
Body measure residual						
Extremity fat	0.87	0.80 – 0.95	0.002	0.86	0.79 – 0.94	0.001
Trunk lean	1.1	0.99 – 1.2	0.082	1.1	0.98 – 1.2	0.13
Extremity lean	1.0	0.94 – 1.1	0.45	0.98	0.90 – 1.1	0.70
BMI	1.0	0.91 – 1.1	0.91	0.94	0.86 – 1.0	0.15
Waist circumference	0.97	0.90 – 1.1	0.54	1.1	0.98 – 1.2	0.11

^{*} >44 IU/L in men or >31 IU/L in women.

[‡] Adjusted for ethnicity, age (6 categories, ordinal), glucose status (doctor-diagnosed diabetes, elevated hemoglobin A_{1C}), serum total cholesterol, cigarette smoking, and alcohol consumption.

[‡] Calculated from logistic regression analysis; per quintile increase in trunk fat and per quintile increase in residuals for the other measures.

[§] Models contained trunk fat and the residual of one of the other body measures. The OR for trunk fat was unchanged regardless of which body measure residual was included in the analysis.