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Intramuscular Fat and Associations with Metabolic Risk Factors in the Framingham Heart Study

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Abstract

Objective—Intramuscular fat accumulates between muscle fibers or within muscle cells. We investigated the association of intramuscular fat with other ectopic fat deposits and metabolic risk factors.

Approach and Results—Participants (n = 2945; 50.2% women; mean age 50.8 years) from the Framingham Heart Study underwent multidetector computed tomography scanning of the abdomen. Regions of interest were placed on the left and right paraspinous muscle and the muscle attenuation (MA) in Hounsfield units were averaged. We examined the association between MA and metabolic risk factors in multivariable models and additionally adjusted for BMI and visceral fat (VAT) in separate models. MA was associated with dysglycemia, dyslipidemia, and hypertension in both sexes. In women, per standard deviation decrease in MA, there was a 1.34 (95% CI 1.10–1.64) increase in the odds of diabetes, a 1.40 (95% CI 1.22 – 1.61) increase in the odds of high triglycerides, and a 1.29 (95% CI 1.12 – 1.48) increase in the odds of hypertension. However, none of these associations persisted after adjustment for BMI or VAT. In men, we observed similar patterns for most risk factors. The exception was metabolic syndrome, which retained association in women even after adjustment for BMI and VAT, and low HDL and high triglycerides in men, whose associations also persisted after adjustment for BMI and VAT.

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Conclusions—MA was associated with metabolic risk factors, but most of these associations were lost after adjustment for BMI or VAT. However, a unique association remained for metabolic syndrome in women and lipids in men.

Keywords

Metabolism; obesity; intramuscular fat; epidemiology

Introduction

Body mass index (BMI) is often used to determine a patient's risk for excess body fat related disease. However, BMI alone does not account for the heterogeneity of health outcomes from obesity.[1] A body of literature exists to investigate the association of different ectopic fat depots in order to better characterize the variety of obesity-related health risks.[2–7] Pericardial, perivascular, and renal sinus fat are associated with the hypothesized local effects of fat,[4–6] whereas visceral adipose tissue (VAT), intrahepatic fat and intramuscular fat are associated with hypothesized systemic effects of adipose tissue.[3;4;7;8]

Intra-muscular fat is of particular interest due to the important role of muscle, particularly skeletal muscle, in insulin-mediated glucose uptake as well as in fat perioxidation.[8] Due to skeletal muscle's high insulin sensitivity and large percentage of body mass, fat accumulation and concomitant loss of insulin sensitivity potentially plays an important role in insulin resistance, obesity, and metabolic syndrome.[8] Previous studies have shown that increased intramuscular fat is associated with decreased insulin sensitivity.[9–14] The reason for this is not entirely understood, although studies have suggested that it may be due to altered action of mitochondrial proteins due to increased lipid peroxidation products.[10]

The current literature on the association between intramuscular fat and metabolic risk factors is limited by relatively small sample sizes (n = 32–173), samples enriched for adiposity,[10;11;14] and often a limited panel of metabolic risk factors focusing on glucose-related factors.[9–14] Finally, these studies generally did not account for potentially confounding factors, most notably BMI or VAT.[9–14] Therefore, the goal of our research was to use a large, community-based cohort to examine the association between intramuscular fat and a comprehensive panel of metabolic risk factors while accounting for potentially confounding factors as well as for BMI and VAT.

Results

Study Sample Characteristics

Study sample characteristics can be found in Table 1. Our sample was middle-aged and half were women. On average, our sample was overweight. Five and a half percent of women had diabetes and 27.1% had metabolic syndrome. The distribution of muscle Hounsfield unit readings for our sample can be seen in Figure 1: the median MA in women was 56 Hounsfield units and for men it was 59 Hounsfield units.

Correlations between Intramuscular Fat and Cardiovascular Disease Risk Factors

Table 2 shows the sex-specific, age-adjusted Pearson correlation coefficients between MA and metabolic parameters. In women, MA was inversely correlated with all of the adiposity measures and metabolic risk factors we examined. That is, as muscle attenuation decreased (which corresponds with a higher level of intra-muscular fat), most metabolic risk factors were more adverse. For men, correlations between MA and metabolic parameters were generally similar to those of the women, but of a smaller magnitude. Among women, the correlation of MA with BMI is −0.26 (R^2 = 6.6%), with VAT −0.48 (R^2 = 23.2%), and with

both, the R^2 = 25.67%. For men, the correlation of MA with BMI is −0.19 (R^2 = 3.73%), with VAT −0.38 (R^2 = 14.7%), and with both, R^2 = 15.72%.

Multivariable-adjusted Associations between MA and Metabolic Risk Factors

MA showed associations with glycemic, lipidemic, and blood-pressure related risk factors in both men and women. We examined these associations in Tables 3 & 4.

Glycemic Risk Factors—In both men and women, MA was inversely associated with all of the glycemic risk factors that we investigated. For example, in women, per 1 standard deviation decrease in MA there was a 2.13 mg/dL increase in plasma glucose. This association persisted after adjustment for BMI (p = 0.014) but not after adjustment for VAT (p = 0.8). Generally, other glycemic associations in women did not persist after adjustment for BMI or VAT with the exception of metabolic syndrome (OR 1.50, p<0.0001 after BMI adjustment; OR 1.22, p=0.03 after VAT adjustment). This association of decreasing MA and increasing metabolic syndrome can even be seen after stratifying the data into VAT and SAT tertiles in Figures 2 and 3, respectively. Figures 2 and 3 examine the HU data within tertiles of VAT in order to examine the association between clinical risk factors and muscle HU within a narrower range of VAT. Results were generally similar but less striking in men.

As MA decreased, insulin resistance in both women and men increased (women: OR 1.27, p=0.001; men: OR 1.04, p=0.5). However, upon adjustment for VAT, we noted that decreasing MA was associated with decreasing odds of insulin resistance (women: OR 0.73, p=0.001; men: OR 0.76, p=0.002). Displayed graphically in Figure 2, we saw a similar stepwise decrease of the prevalence of insulin resistance with decreasing MA within each VAT tertile.

Lipid Risk Factors—As MA decreased, there was an increase in log triglycerides (0.09 per standard deviation decrease in MA, p < 0.0001) and decrease in HDL (−1.54 mg/dL per standard deviation decrease in MA, p = 0.002) in women. After adjustment for BMI, the association with log triglycerides persisted (p = 0.0003), but did not persist after VAT adjustment (p=0.8). In men, we observed the opposite effect. Per standard deviation decrease in MA, there was a non-significant decrease in log triglycerides, even after adjustment for BMI (p=0.003) and VAT (p<0.0001). Displayed graphically in Figure 2, within each VAT tertile, as MA decreased, there was a stepwise decrease in the prevalence of high triglycerides, most prominently in the second VAT tertile. Similar trends were observed for low HDL in men. Both of these trends also persisted when the data was stratified by SAT tertiles instead of VAT tertiles (Figure 3).

Blood-Pressure Related Risk Factors—Blood-pressure related risk factors had less notable associations with MA. In the simple model, we observed associations between decreasing MA and increasing SBP in both women (1.70 mmHg per standard deviation decrease in MA, p = 0.0004) and men (0.97 mmHg per standard deviation decrease in MA, p = 0.03) and similar associations for women with DBP (0.58 mmHg per standard deviation decrease in MA, p = 0.04) and hypertension (1.29 odds per standard deviation decrease in MA, p = 0.0003). However, none of these associations persisted in the BMI or VAT adjusted models.

Framingham Risk Score—In women, per SD decrease in muscle HU, the Framingham Risk Score was higher, even after adjusting for BMI or VAT (Table 3). Similar observations were not observed in men.

Interaction Testing—We observed sex interactions for impaired fasting glucose, metabolic syndrome, log triglycerides, high triglycerides, SBP and DBP. In all cases, the association was stronger in women (Tables 3 and 4). We also tested for age interactions (Supplemental Table I); we observed evidence for age interactions for DBP and insulin resistance, where associations were stronger in the younger group. When stratified by cohort, the results were not materially different (Supplemental Table II).

Discussion

Principal Findings

Our study shows that MA is associated with measures of adiposity including BMI, waist circumference, and VAT as well as metabolic risk factors. These associations were stronger in women, particularly for lipid and blood pressure traits. Overall, most of the associations between MA and metabolic risk factors did not persist after accounting for BMI or VAT, with the exception of metabolic syndrome in women, and HOMA-IR, triglycerides, and HDL in men.

In Context of Current Literature

Prior studies have found, using a diverse set of technology and techniques including NMR spectroscopy,[9;10] that there is an association between increasing intramuscular fat and increasing insulin resistance (and related glycemic parameters).[9–14] Our results without adjustment for BMI or VAT are consistent with this finding.

However, upon adjustment for BMI and VAT, our findings suggest an unexpected association between increasing intramuscular fat and decreasing insulin resistance. The reasons for this remain unclear. Given the correlation between intramuscular fat and generalized and central adiposity, the issue of collinearity is potentially of concern. However, this is unlikely to serve as the sole explanation for the present findings for the following reasons. First, we observed only a modest association between MA and VAT ($r = 0.21 – 0.37$), which is unlikely to result in significant collinearity. Second, when we considered the crude MA data stratified by tertiles of either VAT or SAT, we observed similar unexpected associations between decreasing MA and decreasing insulin resistance. One study has similarly adjusted for VAT and also observed a change in the direction of the association between MA and insulin resistance after accounting for VAT, although the ability to make inferences is limited by the modest sample size ($n = 173$).[12] Other studies have also found an association between high intramuscular fat and high insulin sensitivity in endurance athletes.[15;16] Exercise increases diacylglycerol acyltransferase, which catalyses triglyceride production from diacylglycerol and fatty acyl-CoA and protects against insulin resistance.[17] However, given that our sample is drawn from a community-based study, it is unlikely that this mechanism can explain the present findings.

Similarly, in men after adjustment for VAT, we observed an unexpected directionality of association between decreasing MA and decreasing log triglycerides and increasing HDL. Triglyceride-to-HDL ratio has previously been found to be a useful proxy for insulin resistance in white samples such as ours.[18] Thus, it is of particular interest that we identified paradoxical associations with triglycerides, HDL, and insulin resistance.

Fewer studies have investigated the association between MA and lipid or blood pressure parameters. In 79 men with a BMI ≥ 25 kg/m^2, one study observed inverse correlations between MA and glucose, HOMA-IR, HDL, SBP and DBP, consistent with our findings.[11] We extend the current literature by inclusion of a larger, community-based sample, which

includes women in addition to men, excellent ascertainment of multiple important covariates, and a comprehensive panel of metabolic risk factors.

Potential Mechanisms

Several studies have investigated the physiologic mechanisms of association between intramuscular fat and insulin resistance.[10;19–22] Increased lipid peroxidationmay cause mitochondrial protein modification as well as modification to other proteins along the insulin receptor pathway.[10] This could decrease the sensitivity of the muscle to insulin and lead to insulin resistance.[10] Obesity and diabetes are associated with increased transport of long chain fatty acids into skeletal muscle via an increase in the number of fatty acid translocases.[21] The cause-effect relationship remains uncertain; however, one study did find that after high-fat feeding, mice developed both insulin resistance and increased intramuscular fat in their skeletal muscles.[20] Comparatively, on the same high-fat diet, liver insulin resistance preceded increased intrahepatic fat.[20] Therefore, intramuscular fat may be more closely associated with insulin resistance than other ectopic fats such as intrahepatic fat.

We have consistently observed stronger associations between ectopic fat depots and metabolic risk factors in women as compared to men.[23] While the etiology of this remains uncertain, potential mechanisms include higher rates of delivery of hepatic free fatty acids in women as compared to men,[24] gender differences in fat distribution whereby women have more subcutaneous but less visceral fat as compared to men,[23] and a stronger familial contribution to the distribution of fat in women as compared to men.[25] Whether this can account for the lower relative muscle attenuation in women as compared to men requires further inquiry.

Implications

Our findings emphasize the wide range of associations between MA and metabolic risk factors. Some of these associations persisted even after adjustment or stratification for VAT, an ectopic fat deposit strongly associated with metabolic risk factors.[3;4] While MA is not a measure that could easily be used clinically, these associations have implications for future research. For example, it remains uncertain why there were unexpected trends in the associations of MA for insulin resistance, triglycerides and HDL after accounting for VAT in men. Therefore, further research into these associations and the mechanisms behind them could help to explain the heterogeneity of obesity-related health outcomes. If a proxy for intramuscular fat that is more appropriate for clinical use is later found, these associations could be used to help make metabolic prognoses.

Strengths and Limitations

Strengths of this study include its large sample size, which allowed us to investigate small but potentially significant associations between MA and metabolic risk factors. We identified and adjusted our findings for a number of well-measured potential confounders. Our sample was not drawn from a sample ascertained for obesity or metabolic disease; therefore, our findings are generalizable to a wide population. Our covariates and outcomes were well-documented. Some limitations warrant mention. We used MA as a proxy for intramuscular fat, which is not a direct measurement of intramuscular fat. While this may have lead to misclassification in our sample, it has likely biased our results towards the null, but is unlikely to account for our significant observations. Our sample is also primarily white; therefore the generalizability of our results to other ethnic groups is uncertain. While clinical and computed tomography data in the offspring was not collected contemporaneously; however, our stratified analyses do not suggest that this is an important explanation for our findings. In general, the associations between muscle HU and clinical

risk factors are slightly lower as compared to larger fat depots such as visceral fat. Whether this is due to physiologic reasons of relative metabolic fat activity as compared to the use of a gold standard method of assessment warrants further study. Finally, due to our study's observational and cross-sectional design, causality and temporality cannot be determined from our results.

Conclusions

Intramuscular fat, measured using MA on MDCT, was associated with a wide panel of metabolic risk factors. While some of these associations did not persist after adjustment for BMI and VAT, unique associations remained for metabolic syndrome in women and lipid-related parameters in men. Further investigation into this association may ultimately lead to a better understanding of the heterogeneity of obesity-related health outcomes.

Methods

Study Participants

Participants were derived from the Framingham Heart Study, a cohort study initiated in 1948 with 5209 participants.[1] The offspring of the original participants as well as offspring spouses were recruited to the study in 1971[2] and the third generation and their spouses were recruited in 2002.[3] Participants undergo regular examinations and health history updates.

This study was comprised of Framingham Heart Study offspring and third generation participants who had undergone multidetector computed tomography (MDCT) from 2002–2005. Men were required to be over 35 years of age and women over 40 years. Participants weighing >160 kg did not undergo MDCT due to weight restrictions. Of the 3529 participants who underwent CT scanning, 3127 had muscle attenuation (MA) measurements. Of the 3127, 2945 had a complete set of covariates and were included in the final analysis (1479 women, 1466 men). Of those final analysis participants without diabetes (1398 women, 1365 men), 1280 women and 1277 men had insulin data available and were included in analyses of HOMA-IR and insulin resistance.

Measurement of Muscle Attenuation and Visceral and Subcutaneous Fat

Participants underwent abdominal CT imaging while in a supine position. As previously described, an eight-slice MDCT (LightSpeed Ultra, General Electric, Milwaukee, WI, USA) was used to image 25 contiguous 5-mm thick slices (120 kVp, 400 mA, 500 ms gantry rotation time, 3:1 table feed).[4] One hundred and twenty-five millimeters above S1 level were covered by the scan.

A ~1 cm region of interest was placed on both the left and right paraspinous muscles at mid-abdomen level. The MA of these two areas were averaged in order to calculate mean MA; the correlation between the two reads is 0.86. The inter-reader correlation was 0.88. We focused on paraspinous muscles due to their slow-twitch characteristics, which tend to have more intramuscular fat than fast-twitch muscles.[5;6] Skeletal MA on MDCT scans to evaluate intramuscular fat has been previously validated by muscle biopsy study.[7] In vivo vastus lateralis MA via MDCT had a Pearson correlation coefficient of −0.43 ($P<0.01$, $n=45$) with vastus lateralis muscle fiber lipid content (% area) determined with histochemical staining of lipid after biopsy.[7]

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volumes were determined via manual tracing of the abdominal muscular wall on 25 continuous 5 mm slices from an eight-slice MDCT scan of the abdomen. The window for fat was −195 to −45 Hounsfield units with a window center of −120 Hounsfield units. All fat outside of the

manual tracing was defined as SAT while that inside of the tracing was defined as VAT. The inter-reader correlation for SAT was 0.997 and for VAT was 0.992.[8]

Cardiovascular Disease Risk Factor Assessment

Risk factors for this study were determined at the seventh offspring examination (1998–2001) and the first third generation examination (2002–2005). Fasting glucose and lipids were measured after an overnight fast. Impaired fasting glucose (IFG) was defined as 100–125 mg/dL fasting plasma glucose for participants not on diabetes treatment. Diabetes (DM) was classified as fasting plasma glucose of ≥ 126 mg/dL or current use of insulin or a hypoglycemic treatment. The modified Adult Treatment Panel III criteria was used to classify metabolic syndrome.[9] Insulin was calculated via radioimmunoassay (Offspring Cohort) and ELISA (Third Generation cohort). Third Generation cohort insulin values were standardized to the values of the Offspring Cohort in order to account for the different insulin calculation methods.[10] HOMA-IR was determined by fasting glucose multiplied by fasting insulin divided by 22.5.[11] Insulin resistance (IR) was classified as the top quarter of HOMA-IR in participants without diabetes.[12] High TG was classified as ≥150 mg/dL or if the participant was on lipid-lowering medication. Low HDL was defined as HDL < 50 mg/dL for women and <40 mg/dL for men. Blood pressure was determined by averaging two reads taken at rest with a mercury column sphygmomanometer. Hypertension (HTN) was determined by systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg or current use of hypertension treatment medication.

Measurement of Covariates

Participants were designated as current smokers if they had smoked ≥ 1 cigarette per day in the year prior to examination. Alcohol use was determined via a physician-administered questionnaire. Participants were split into two alcohol use groups based on whether they had > 7 drinks/week for women or > 14 drinks/week for men. Physical activity was calculated on the physical activity index (PAI) after a physician-administered questionnaire concerning the average number of hours of sleep and sedentary, slight, moderate and heavy activity the participant took part in per day. Women without menstrual bleeding for ≥ 1 year were considered postmenopausal. BMI was determined by participant weight in kilograms divided by the square of participant height in meters. Waist circumference was calculated at the level of the umbilicus.

Statistical Analysis

MA approximated the normal distribution for both women and men. Logs of triglycerides and HOMA-IR were performed to normalize their distributions. Sex-specific, age-adjusted correlations between MA and metabolic risk factors were calculated.

For continuous risk factors, multivariable-adjusted linear regression models were used to model the relative change in the outcome per one standard deviation decrease in MA (i.e., more intra-muscular fat). For dichotomous risk factors, a multivariable-adjusted logistic model was used. Three sex-specific models were fit separately for each of the following outcomes: plasma glucose, log HOMA-IR, insulin resistance, impaired fasting glucose, diabetes, metabolic syndrome, log triglycerides, high triglycerides, HDL, low HDL (<40 mg/dl in men and <50 mg/dl in women), SBP, DBP, and hypertension. In the first model, covariates included age, current smoking status, alcohol use, physical activity, treatment for hypertension (for SBP and DBP models), dyslipidemia (for triglyceride and HDL models), and diabetes (for glucose models) as well as menopausal status and hormone replacement therapy in models in women. The second model additionally adjusted for BMI. The third model additionally adjusted for VAT (but not for BMI).

The Framingham Risk score was calculated as previously described[13] and examined in association with muscle HU among participants free of clinical CVD.

Given previously observed interactions with sex, we tested the interactions between MA and sex; we also examined the interaction with age and metabolic risk factors. We also stratified our results by cohort to test whether the lack of temporality between the offspring clinical risk factor data and the computed tomography scans might impact the results.

Analyses were calculated with SAS version 9.2. P-values less than 0.05 were considered statistically significant for primary analyses. Because of the many interactions that we tested, we used a significance level of 0.01 to assess the significance of interaction terms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Selected Abbreviations

MDCT	multidetector computed tomography
HOMA-IR	homeostatic model assessment insulin resistance
VAT	visceral adipose tissue
SAT	subcutaneous adipose tissue
SBP	systolic blood pressure
DBP	diastolic blood pressure
DM	diabetes
IR	insulin resistance
IFG	impaired fasting glucose
HTN	hypertension
MetS	metabolic syndrome
ELISA	enzyme-linked immunosorbent assay
OR	odds ratio
MA	muscle attenuation
BMI	body mass index

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Significance

Heterogeneity of obesity-related health risks is increasingly recognized. Body mass index (BMI) does not fully account for the differential associations of ectopic fat depots with health outcomes. Intramuscular fat accumulates between muscle fibers (interstitial fat) or within muscle cells (intramyocellular lipids). We investigated the association of intramuscular fat with other ectopic fat deposits and metabolic risk factors using participants from the Framingham Heart Study. We estimated intra-muscular fat by measuring muscle attenuation in the left and right paraspinous muscle, and examined its association with metabolic risk factors. We found that higher levels of intramuscular fat were associated with abnormal levels of glucose, lipids, and blood pressure. While most of these associations were due to levels of overall body fatness, the presence of the metabolic syndrome was associated with higher levels of intra-muscular fat even when we accounted for body mass index.

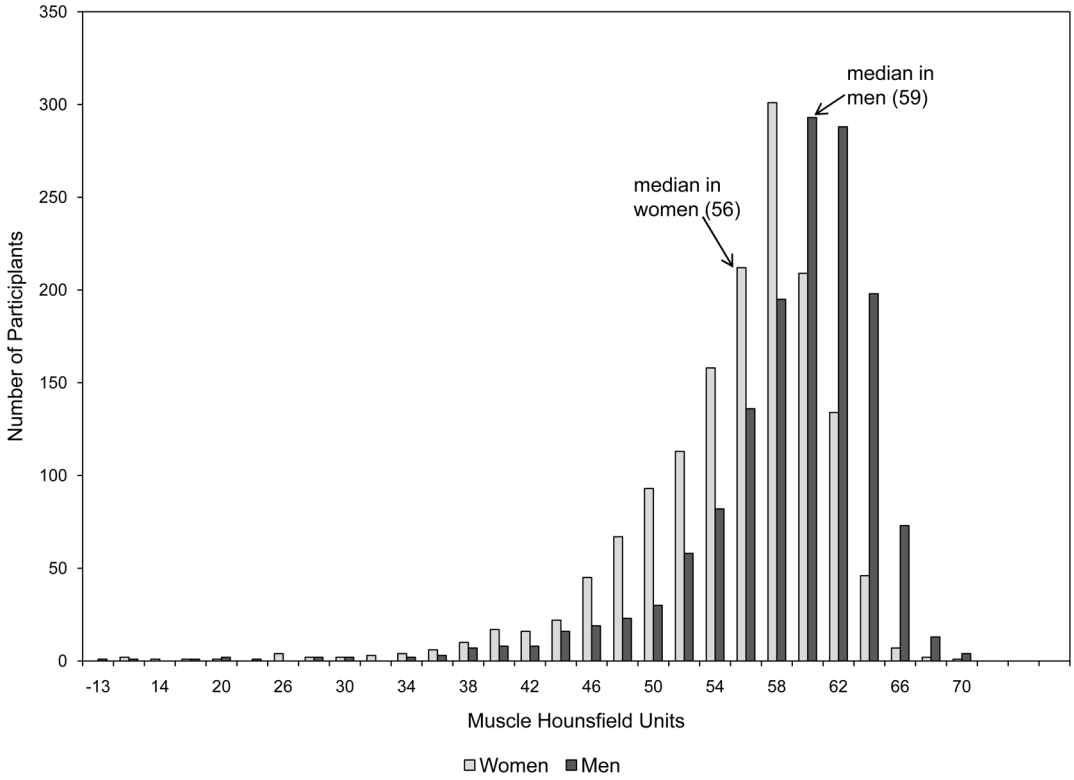

Figure 1.
Distribution of Muscle Hounsfield Units

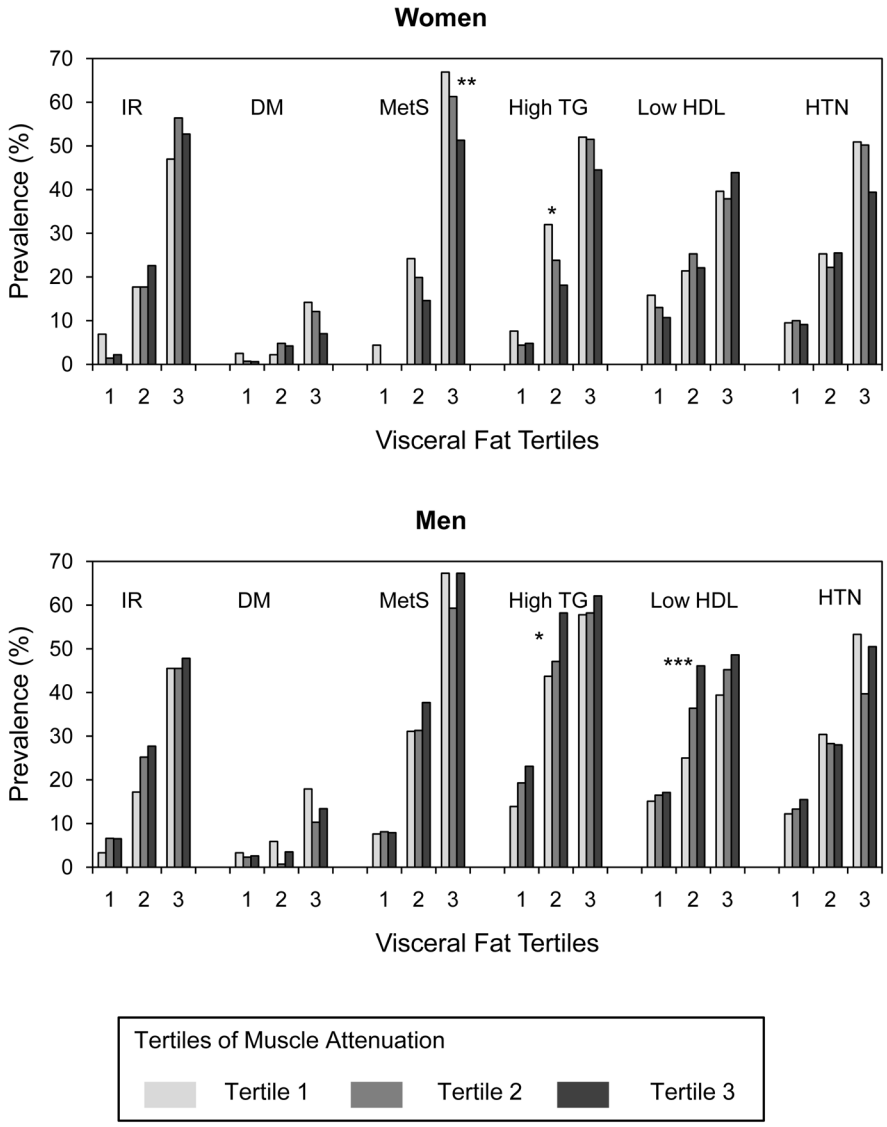

Figure 2.

Age-adjusted Metabolic Risk Factors by Muscle Tertiles within VAT Tertiles.
*p<0.05, **p<0.01, ***p<0.001
IR = insulin resistance, DM = diabetes, MetS = metabolic syndrome, High TG = high triglycerides, Low HDL = low high density lipoprotein, HTN = hypertension

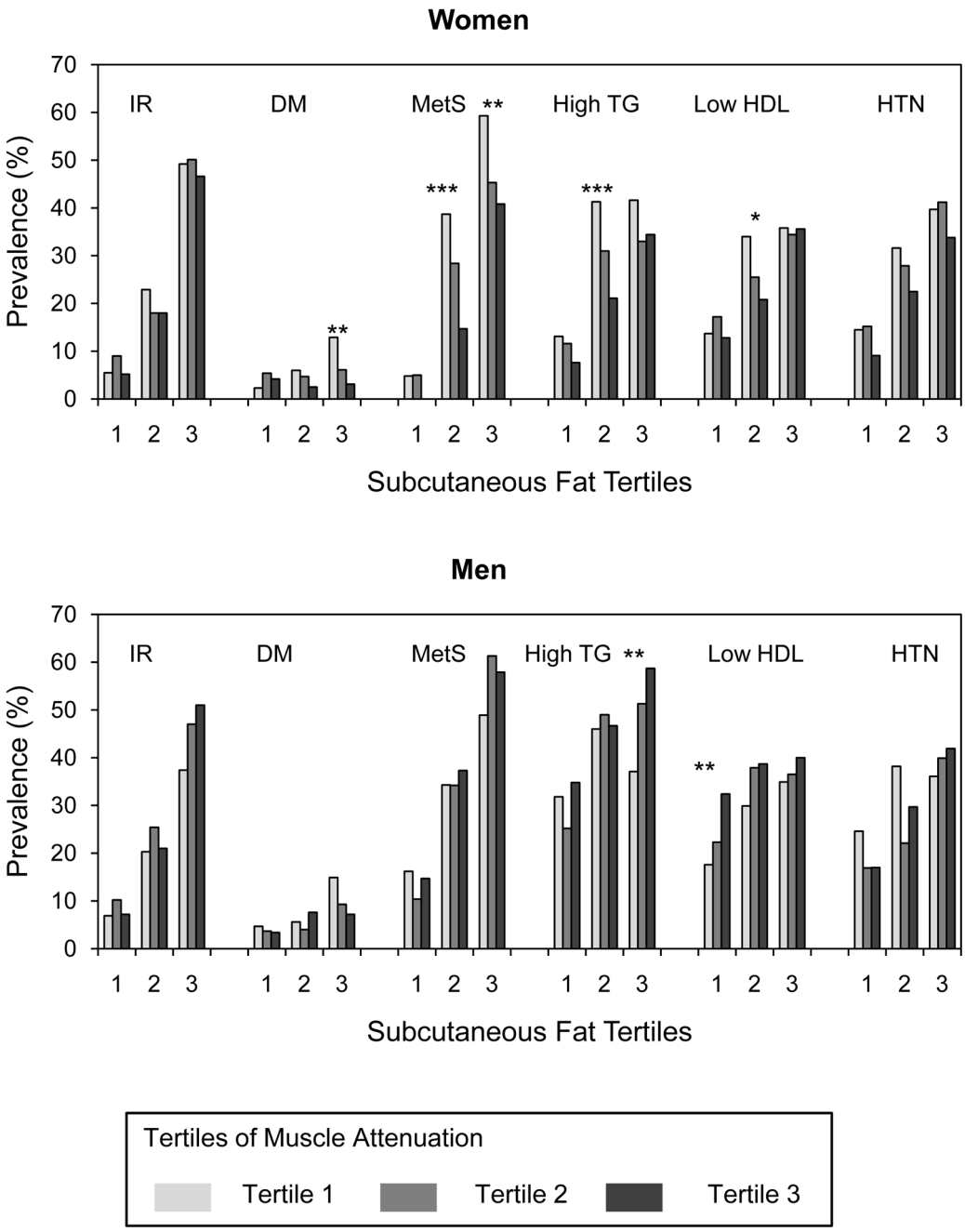

Figure 3.

Age-adjusted Metabolic Risk Factors by Muscle Tertiles within SAT Tertiles

*p<0.05, **p<0.01, ***p<0.001

IR = insulin resistance, DM = diabetes, MetS = metabolic syndrome, High TG = high triglycerides, Low HDL = low high density lipoprotein, HTN = hypertension

Table 1

Study Sample Characteristics

Category	Women (n = 1479)	Men (n = 1466)
Age (years)	52.0 (9.8)	49.6 (10.7)
BMI (kg/m^2)	26.9 (5.7)	28.1 (4.5)
Waist Circumference (cm)	92.9 (15.4)	100.0 (11.7)
Current Smoking (%)	12.0 (177)	13.8 (203)
Alcohol Use (%)	15.0 (222)	16.3 (239)
Physical Activity (PAI)	36.8 (5.8)	38.5 (8.3)
Postmenopausal (%)	50.8 (751)	NA
Current Hormone Replacement (%)	19.5 (288)	NA
VAT (cm^3)	1348.8 (832.4)	2175.8 (1030.6)
SAT (cm^3)	3111.1 (1500.1)	2538.0 (1160.0)
Muscle (HU)	54.4 (6.4)	57.9 (6.3)
Muscle* (HU)	56.0 (51.5 – 58.5)	59.0 (56.0 – 61.5)
Fasting Glucose (mg/dl)	95.8 (18.2)	102.0 (24.5)
Impaired Fasting Glucose (%)	18.5 (273)	36.4 (534)
HOMA-IR*$^+$	2.4 (2.0 – 3.05)	2.7 (2.2 – 3.5)
Diabetes (%)	5.5 (81)	6.9 (101)
Diabetes Treatment (%)	3.0 (44)	3.5 (51)
Triglycerides (mg/dl)*	94.0 (66.0 – 1400.0)	113.0 (76.0 – 171.0)
High Triglycerides (%)	26.7 (395)	42.4 (622)
HDL Cholesterol (mg/dl)	61.3 (16.9)	46.2 (12.6)
Low HDL Cholesterol (%)	25.5 (377)	32.1 (470)
Lipid Treatment (%)	10.3 (152)	17.0 (249)
Systolic Blood Pressure (mmHg)	120.2 (17.7)	123.1 (14.7)
Diastolic Blood Pressure (mmHg)	73.5 (9.2)	77.7 (9.1)
Hypertensive (%)	26.6 (394)	29.9 (439)
Hypertensive Treatment (%)	18.7 (277)	17.9 (263)
Metabolic Syndrome (%)	27.1 (401)	35.2 (516)

Data are presented as mean (SD) for continuous traits, and count (n) for categorical data *Data presented as Median (1st Quartile, 3rd Quartile)

$^+$For HOMA-IR data, data are presented among those without diabetes, N=1280 for women, N=1277 for men

Table 2

Age-adjusted Correlation Coefficients between Muscle Attenuation and Measures of Adiposity and Metabolic Risk Factors

Metabolic Parameters	Muscle Attenuation	
	Women	Men
Age	−0.53***	−0.57***
BMI	−0.22***	−0.15***
Waist Circumference	−0.27***	−0.17***
VAT	−0.37***	−0.21***
SAT	−0.23***	−0.15***
Glucose	−0.14***	−0.08**
Log HOMA-IR+	−0.09***	0.009
Log Triglycerides	−0.18***	0.01
HDL	0.08**	−0.06*
Systolic Blood Pressure	−0.11***	−0.08**
Framingham Risk Score	−0.14***	−0.07***

Data are presented as: Correlation Coefficient (N)

* Designates p-value < 0.05

** Designates p-value < 0.01

*** Designates p-value < 0.001

+ For HOMA-IR data, data are presented among those without diabetes, N=1280 for women, N=1277 for men

Table 3

Multivariable-adjusted Associations between Muscle Attenuation and Continuous Metabolic Risk Factors modeled per 1 SD decrease in muscle HU

	Model	Women		Men		
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Sex Interaction p-value
Glucose						0.6
	Simple	2.13 (1.28, 2.99)	<0.0001	2.11 (0.76, 3.46)	0.002	
	+BMI	1.06 (0.22, 1.90)	0.014	1.31 (−0.03, 2.65)	0.06	
	+VAT	0.12 (−0.75, 0.99)	0.8	1.22 (−0.14, 2.59)	0.08	
Log HOMA-IR						0.10
	Simple	0.05 (0.02, 0.07)	0.0004	−0.00 (−0.03, 0.03)	0.98	
	+BMI	−0.01 (−0.03, 0.02)	0.6	−0.403 (−0.06, −0.01)	0.003	
	+VAT	−0.04 (0.07, −0.02)	0.0003	−0.06 (−0.08, −0.03)	<0.0001	
Log Triglycerides						<0.0001
	Simple	0.09 (0.07, 0.12)	<0.0001	−0.01 (−0.05, 0.02)	0.5	
	+BMI	0.05 (0.02, 0.08)	0.0003	−0.04 (−0.08, −0.01)	0.01	
	+VAT	0.00 (−0.02, 0.03)	0.8	−0.07 (−0.10, −0.03)	0.0002	
HDL						0.103
	Simple	−1.54 (−2.51, −0.57)	0.002	0.59 (−0.17, 1.35)	0.1	
	+BMI	−0.24 (−1.20, 0.71)	0.6	1.29 (0.56, 2.03)	0.0006	
	+VAT	0.95 (−0.03, 1.93)	0.06	1.73 (1.00, 2.46)	<0.0001	
SBP						<0.0001
	Simple	1.70 (0.76, 2.65)	0.0004	0.97 (0.11, 1.83)	0.03	
	+BMI	0.71 (−0.23, 1.65)	0.13	0.47 (−0.38, 1.32)	0.3	
	+VAT	0.05 (−0.94, 1.03)	0.9	0.31 (−0.55, 1.17)	0.5	
DBP						0.002
	Simple	0.58 (0.04, 1.13)	0.04	0.11 (−0.45, 0.67)	0.7	
	+BMI	0.03 (−0.52, 0.57)	0.9	−0.26 (−0.81, 0.30)	0.4	
	+VAT	−0.35 (−0.92, 0.21)	0.2	−0.44 (−1.00, 0.12)	0.12	
Framingham Risk Score						<0.0001
	Simple	0.008 (0.005, 0.011)	<.0001	0.004 (−0.0002, 0.009)	0.06	

	Model	Women		Men		Sex Interaction p-value
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	
	+BMI	0.004 (0.001, 0.007)	0.005	0.0009 (−0.003, 0.005)	0.69	
	+VAT	0.0004 (−0.003, 0.003)	0.80	−0.001 (−0.005, 0.003)	0.64	
	+SAT	0.005 (0.002, 0.008)	0.0006	0.002 (−0.002, 0.007)	0.30	

Note: Data presented include effect size expressed per 1 standard deviation decrease in muscle attenuation with 95% confidence intervals.

*All models are adjusted for: age, current smoking status, alcohol use, and physical activity. Menopausal status and hormone replacement therapy are also included for in models among women.

**Additional covariate in SBP and DBP model: Hypertension Treatment; Additional covariate in HDL and TG models: Lipid Lowering Treatment; Additional covariate for FPG: Treatment for Diabetes.

Table 4

Multivariable-adjusted Associations of Metabolic Risk Factor Odds Ratios with Muscle Attenuation

	Model	Women		Men		
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Sex Interaction p-value
Insulin Resistance						0.09
	Simple	1.27 (1.10, 1.47)	0.001	1.05 (0.90, 1.22)	0.6	
	+BMI	0.95 (0.80, 1.14)	0.6	0.84 (0.70, 1.02)	0.08	
	+VAT	0.72 (0.59, 0.88)	0.001	0.75 (0.62, 0.90)	0.002	
IFG						0.003
	Simple	1.31 (1.13, 1.50)	0.0002	1.05 (0.92, 1.19)	0.5	
	+BMI	1.14 (0.98, 1.32)	0.10	0.98 (0.86, 1.12)	0.8	
	+VAT	0.98 (0.83, 1.16)	0.9	0.94 (0.82, 1.07)	0.3	
DM						0.2
	Simple	1.34 (1.10, 1.64)	0.004	1.26 (1.06, 1.51)	0.009	
	+BMI	1.16 (0.93, 1.45)	0.2	1.12 (0.93, 1.35)	0.2	
	+VAT	0.95 (0.74, 1.21)	0.7	1.14 (0.94, 1.37)	0.2	
Metabolic Syndrome						<0.0001
	Simple	1.85 (1.58, 2.15)	<0.0001	1.10 (0.96, 1.26)	0.2	
	+BMI	1.50 (1.27, 1.77)	<0.0001	0.89 (0.76, 1.03)	0.12	
	+VAT	1.22 (1.02, 1.45)	0.03	0.80 (0.68, 0.94)	0.006	
High Triglycerides						<0.0001
	Simple	1.40 (1.22, 1.61)	<0.0001	0.91 (0.80, 1.03)	0.15	
	+BMI	1.24 (1.07, 1.43)	0.004	0.81 (0.71, 0.94)	0.004	
	+VAT	1.05 (0.89, 1.23)	0.6	0.75 (0.65, 0.86)	<0.0001	
Low HDL						0.04
	Simple	1.17 (1.02, 1.34)	0.02	0.85 (0.74, 0.99)	0.04	
	+BMI	1.01 (0.87, 1.17)	0.9	0.75 (0.64, 0.88)	0.0005	
	+VAT	0.86 (0.73, 1.02)	0.08	0.70 (0.59, 0.82)	<0.0001	
HTN						0.02
	Simple	1.29 (1.12, 1.48)	0.0003	1.10 (0.95, 1.26)	0.2	

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	Model	Women		Men		Sex Interaction p-value
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	
	+BMI	1.11 (0.96, 1.29)	0.2	0.99 (0.86, 1.14)	0.9	
	+VAT	0.98 (0.84, 1.15)	0.8	0.95 (0.82, 1.09)	0.5	

Note: Data presented include odds of the condition per 1 standard deviation decrease in muscle attenuation with 95% confidence interval.

*All models are adjusted for: age, current smoking status, alcohol use, and physical activity. Menopausal status and hormone replacement therapy are also included for in models among women.