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Association Between Visceral and Subcutaneous Adipose Depots and Incident Cardiovascular Disease Risk Factors

Tobin M. Abraham, MD^{1,2}, Alison Pedley, PhD², Joseph M. Massaro, PhD³, Udo Hoffmann, MD⁴, and Caroline S. Fox, MD, MPH^{1,2}

¹National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA and the National Heart, Lung, and Blood Institute, Bethesda, MD

²Department of Endocrinology, Hypertension and Diabetes, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

³Department of Biostatistics, Boston University School of Public Health, Boston, MA

⁴Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Visceral and subcutaneous adipose tissue (VAT and SAT) vary in volume and quality. We evaluated whether fat volume or attenuation (indirect measure of quality) predicts metabolic risk factor changes.

Methods and Results—Framingham Heart Study Multi-detector Computed Tomography Substudy participants (n=1730, 45% women) were followed over a mean of 6.2 years. Baseline VAT and SAT volume (in cm³) and attenuation (in Hounsfield units, HU) were assessed. Outcomes included blood pressure, lipids and glucose. We constructed multivariable regression models predicting change from baseline to follow-up. Baseline VAT was associated with metabolic risk factors at follow-up. Per 500 cm³ increment in baseline VAT, glucose was 2.34 mg/dL higher (95% CI 1.71–2.97) and HDL was 1.62 mg/dL lower (95% CI 0.97–2.28) in women (p<0.0001 for both). These findings remained significant after adjustment for BMI. Results for SAT were similar, although less striking. Lower (more negative) fat attenuation was associated with more adverse metabolic profiles at follow-up. For example, per 5 unit decrease in baseline VAT HU, log triglycerides increased by 0.08 mg/dL (95% CI 0.05–0.12, p=0.005), which remained significant after adjustment for baseline VAT. Among men, VAT and SAT HU were associated with changes in CVD risk factors, but were mostly attenuated after baseline volume adjustment.

Conclusions—VAT and SAT volume are associated with incident metabolic risk factors beyond their contributions to overall adiposity. Decrements in fat attenuation are also associated with incident risk factors. These findings suggest that both volume and quality of VAT and SAT contribute to metabolic risk.

Correspondence: Caroline S. Fox MD MPH, Framingham Heart Study, 73 Mt Wayte Ave Suite #2, Framingham MA 01702, Phone: 617-732-6987, Fax: 617-515-9194, foxca@nhlbi.nih.gov.

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Keywords

Epidemiology; Population; Prevention; Adipose Depots

Introduction

VAT and SAT are distinct adipose depots that can be quantified using advanced radiographic techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). While not routinely measured clinically, both VAT and SAT have been correlated with metabolic risk factors. In particular, VAT is associated with insulin resistance and markers of oxidative stress and inflammation.^{1–4} Obesity is known to be a heterogeneous condition, and metabolic risk can vary widely among obese individuals.⁵ A better understanding of the risks associated with distinct adipose depots may help explain some of this heterogeneity.

While both VAT and SAT are associated with an adverse metabolic risk profile, less is known about whether VAT or SAT predict future development of cardiovascular risk factors. Prior work has suggested that VAT, but not SAT or total fat mass predicted incident diabetes.⁶ VAT has been reported to predict development of cardiovascular disease or risk factors among certain ethnicities or specific age groups.^{7–9} Moreover, whether fat quality in different depots contributes to incident metabolic risk factors has not been widely explored. Large prospective studies evaluating both the volume and quality of distinct fat depots and their associations with development of metabolic risk factors are lacking. Thus, we sought to evaluate whether VAT or SAT volume and attenuation (as an indirect measure of fat quality) predicts development of a broad array of traditional cardiovascular risk factors over and above what is accounted for by BMI in a large population-based study.

Research Methods

Study Participants

The Framingham Heart Study is a longitudinal study of cardiovascular risk factors that began in 1948 with the enrollment of the original cohort.^{10, 11} Participants included in the current study were drawn from a subset of the Third Generation cohort that underwent multi-detector computed tomography (MDCT) scanning. A total of 1765 Third Generation participants who underwent MDCT and attended both exam 1 (2002–2005) and exam 2 (2008–2011) were included; the median time between CT exams was 6.2 years with an interquartile range of 6.0–6.4 years. After excluding individuals with missing MDCT measures or missing covariates, a total sample of 1730 (45% women) was available for analysis. Participants gave written informed consent; the FHS procedures and protocols were approved by the Institutional Review Boards at the Boston University Medical Center and the Massachusetts General Hospital.

VAT and SAT Measurements

Participants underwent MDCT of the chest and abdomen using Discovery VCT 64-slice PET/CT scanner (GE Healthcare). Thirty contiguous 5-mm thick slices (120kVP; 100–

300mA dependent on BMI) were acquired, beginning 2 cm above the S1 vertebra. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes were measured using the Aquarius 3D Workstation (TeraRecon Inc., San Mateo, CA). SAT and VAT attenuation in Hounsfield units (HU) were measured using a previously described protocol.¹² Briefly, the abdominal muscular wall separating the visceral and subcutaneous compartments was traced manually, and fat tissue was identified by HU attenuation between -195 and -45. Average HU of each fat depot generated the fat attenuation measure. In a previous study, our group reported high inter-reader and intra-reader correlation (0.997 for SAT, 0.992 for VAT).¹³

Metabolic Risk Factor Assessment

Metabolic risk factors were assessed at baseline and follow-up examinations. Seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured as part of the physician examinations. Plasma glucose, HDL cholesterol and triglycerides were measured on fasting blood samples.

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or on treatment. Hypertriglyceridemia was defined as triglycerides ≥ 150 mg/dL or on lipid-lowering treatment. Low HDL was defined as < 40 mg/dL in men or < 50 mg/dL in women. Type 2 diabetes was defined as a fasting glucose ≥ 126 mg/dL or on diabetes treatment. Metabolic syndrome was defined using modified Adult Treatment Panel III criteria.¹⁴

Covariate Assessment

Covariates were measured at the baseline exam. Height, weight and waist circumference at the level of the umbilicus were measured on site as part of each examination cycle. BMI was calculated as the weight in kilograms divided by the square of the height in meters. A technician-administered physical activity questionnaire yielded a physical activity index based on average number of hours of daily sleep and level of reported activity (sedentary, slight, moderate or high). Alcohol intake was assessed at the physician interview; moderate to heavy alcohol intake was defined as > 14 drinks/week in men and > 7 drinks/week in women. Participants were considered current smokers (if they had smoked at least 1 cigarette per day for the previous year), former smokers or never smokers. Women were classified as being menopausal if they had no menstrual bleeding for at least 1 year. Use of hormone replacement was assessed at the physician interview.

Statistical Analysis

We constructed sex-specific linear regression models predicting changes in systolic and diastolic blood pressure (SBP and DBP), fasting glucose, log transformed triglycerides and HDL-cholesterol. Estimates are given per 500 cm³ increment in SAT or VAT volume. For each metabolic risk factor, a multivariable model (Model 1) adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (women only), and hormone replacement therapy (women only). A second model additionally adjusted Model 1 for BMI. The SBP and DBP models excluded individuals on anti-hypertensive medications at baseline; 73/771 women [9.5%] and 110/958 men [11.5%] were excluded. We added 10 mm

Hg to the follow up value of SBP and 5 mm Hg to the follow up value of DBP if a participant was on anti-hypertensive medications at follow up.¹⁵ At follow-up, 78/698 women (11.2%) and 133/848 men (15.7%) reported use of anti-hypertensive medication. The glucose model excluded participants on diabetes medications at baseline; 11 of 772 women (1.4%) and 20 of 954 men (2.1%) were excluded due to use of diabetes medications at baseline. The triglyceride model excluded participants with hypertriglyceridemia at baseline; 40 of 772 women (5.2%) and 133 of 954 men (13.9%) were excluded due to use of lipid-lowering medication at baseline. Similar imputation methods for glucose and lipids do not exist and therefore were not used. The HDL model excluded participants with low HDL at baseline. Sex-interaction p-values were calculated for each outcome. Due to exclusions based on the baseline parameters, the sample sizes varied for each outcome.

Sex-specific logistic regression models were also constructed predicting incidence at the follow-up examination of diabetes, hypertension, low HDL, hypertriglyceridemia and metabolic syndrome for a 500 cm³ increment in baseline SAT or VAT volume. For each outcome, a multivariable model (Model 1) adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (women only) and hormone replacement therapy. A second model additional adjusted Model 1 for BMI. The hypertension model was additionally adjusted for baseline SBP and baseline DBP. The diabetes model was additionally adjusted for baseline fasting glucose. Low HDL models and hypertriglyceridemia models were additionally adjusted for baseline HDL and baseline log triglycerides, respectively.

For the same outcomes described above, sex-specific linear and logistic regression models were also constructed predicting outcomes based on a 5 HU decrement in baseline fat attenuation. A multivariable model (Model 1) was constructed identical to the modeling structures described above for fat volume. A second model adjusted Model 1 for the corresponding fat volume.

All statistical analyses were conducted using SAS version 9.3. A two-sided 0.05 level of significance was used to declare statistical significance; there were no adjustments made for multiple comparisons.

Results

Study Sample Characteristics

Sex-specific baseline characteristics of study participants are shown in Table 1. Of the 1730 included individuals, nearly half (45%) were women. Mean age at baseline was 46.0 years among women and 44.1 years among men. Mean BMI was in the overweight range for both women and men.

Fat volume and Incident CVD Risk Factors

Results of sex-specific linear and logistic regression models predicting changes in metabolic parameters from VAT and SAT volume are shown in Tables 2 and 3.

Among women, baseline VAT volume was associated with incident increases in metabolic risk factors. For example, for each additional 500 cm³ in baseline VAT, we observed a 2.34 mg/dL increase in fasting glucose from baseline to follow up (95% CI 1.71–2.97), and a 1.62 mg/dL decrease in HDL-cholesterol (95% CI 0.97–2.28) ($p < 0.0001$ for both) at follow-up. For each additional 500 cm³ in VAT at baseline, the odds of the metabolic syndrome were 2.58 times higher (95% CI 2.05–3.25, $p < 0.0001$). In most cases, significance persisted after BMI adjustment.

In men, increased baseline VAT volume was also associated with higher odds of several incident risk factors. We observed higher odds of hypertension (OR 1.28, 95% CI 1.12–1.47) and metabolic syndrome (OR 1.70, 95% CI 1.45–1.98) ($p < 0.001$ in both cases) for every 500 cm³ increment in VAT volume, and for these outcomes, the findings persisted after BMI adjustment. Baseline SAT volume was associated with changes in some risk factors over time among women. For example, each additional 500 cm³ increment in baseline SAT volume was associated with a 0.96 mm Hg increase in SBP (95% CI 0.65–1.28, $p < 0.0001$), and a 0.55 mm Hg increase in DBP (95% CI 0.35–0.76, $p < 0.0001$). For each 500 cm³ increment in baseline SAT volume, the odds of hypertension at follow-up was 1.16 times higher (95% CI 1.06–1.26, $p = 0.001$). These blood pressure increases among women persisted after BMI adjustment. Among men, increments in baseline SAT volume were not associated with significant changes in risk factors over time.

Tests for sex interaction were significant for several outcomes, and uniformly the associations between each fat exposure and outcomes were more adverse among women (Tables 2 and 3). For example, a significant sex-interaction was detected for HDL-cholesterol predicted by baseline VAT volume ($p = 0.01$, Table 2), whereby the results were stronger in women (per 500 cm³ increment in VAT volume, HDL-cholesterol was 1.62 mg/dL lower among women at follow up versus 0.44 mg/dL lower among men at follow up).

Fat Attenuation and Incident Risk Factors

Results of sex-specific linear and logistic regression models for fat attenuation are shown in Tables 4 and 5. Among women, lower fat attenuation was associated with a more adverse metabolic profile at follow-up. For example, for a 5 unit decrease in VAT HU at baseline, we observed a 0.08 mg/dL increase in log triglycerides (95% CI 0.05–0.12, $p = 0.005$) at follow up. For a 5 unit decrease in SAT HU at baseline, we observed a 2.19 mm Hg increase in SBP (95% 1.35–3.03, $p < 0.0001$). These findings remained significant after adjustment for baseline fat volume. Among men, VAT HU and SAT HU were associated with changes in risk factors including SBP and glucose from baseline to follow up, however these changes were attenuated after adjusting for baseline fat volume. In secondary analyses adjusting the fat attenuation models for either VAT or BMI, the results were generally similar to the fat attenuation models adjusted for the corresponding fat volume only (Supplementary Tables 1 and 2).

Several sex interactions were noted in the regression models predicting changes based on fat attenuation (Tables 4 and 5). The sex-specific models suggested that the changes in risk factors per decrement in fat attenuation were more pronounced among women. For example,

significant sex interactions were detected between fat attenuation (both SAT HU and VAT HU) and HDL-cholesterol ($p < 0.001$ and $p < 0.05$, respectively); in the sex-specific models, HDL-cholesterol decreased more among women than among men per 5 HU decrement in fat attenuation.

Figures 1 and 2 depict sex-specific baseline prevalence of selected risk factors stratified by VAT attenuation tertiles and SAT attenuation tertiles, respectively, within BMI categories (normal, overweight or obese). Figure 1 shows a general pattern of higher baseline prevalence of risk factors among the lowest VAT attenuation tertiles within each BMI category. This pattern is less pronounced for SAT attenuation.

Discussion

Principal Findings

Our principal findings are threefold. First, higher VAT volume is associated with the development of cardiovascular risk factors over time, and BMI did not fully account for these associations. Second, higher SAT volume is associated with incident risk factors, particularly among women, and these associations are not fully explained by BMI. Third, lower VAT and SAT attenuation, as indirect measures of fat quality, are associated with development of an adverse risk profile. Fat volume did not fully account for the associations of fat attenuation with incident risk factors.

In the context of the current literature

The present study prospectively examined the association between both fat volume and attenuation and incident metabolic risk factors. Our results expand upon prior work that has shown associations between VAT volume and incident metabolic risk. Published studies have shown a correlation between VAT volume and incidence of type 2 diabetes,^{6, 8} hypertension⁷ and dyslipidemia.¹⁶ Our findings were observed in both women and men. We robustly assessed and adjusted for a number of possible confounders. The association between VAT and metabolic risk factors persisted after BMI adjustment, further supporting the idea that VAT is a unique pathogenic depot that confers risk beyond its contribution to overall adiposity.

There is less published data about incident associations of SAT volume. A recent study of 732 obese adults divided participants into tertiles of SAT volume and found no trend for incident diabetes with increasing SAT.⁶ In the present study, we observed associations between SAT and several incident risk factors, particularly among women. These findings relate in part to our larger sample size, which lends better power to detect differences, and our robust assessment of an array of risk factors.

Fat quality in association with metabolic risk has been less extensively explored than fat volume. We have previously shown that lower VAT and SAT attenuation (i.e. more negative HU) was cross-sectionally associated with a more adverse metabolic profile even after adjustment for absolute fat volume.¹² The results from the present study extend these findings to suggest that measurement of fat quality can predict future development of

metabolic risk factors, and that for women, fat quality is predictive of selected incident CVD risk factors beyond fat volume alone.

Potential mechanisms

The unique pathogenic property of VAT, beyond its contributions to overall adiposity, may be due its role as an endocrine organ secreting adipokines that contribute to inflammation and insulin resistance. It is known that macrophages infiltrate VAT, leading to inflammation.^{17, 18} It is also known that VAT secretes a more pro-inflammatory cytokine profile than SAT, characterized by higher TNF-alpha and other pro-inflammatory molecules.¹⁹

The observation that SAT is associated with metabolic risk factors is partly explained by its contribution to overall adiposity. Our observation that, in women, SAT may have adverse metabolic effects beyond overall adiposity may be partly due to the fact that women have a wider baseline range of SAT volume compared to men (shown in Table 1). This wider range at baseline allows for better detection of differences based on SAT volume.²⁰ Thus any unique pathogenic properties are likely to be more pronounced. For example serum leptin levels are more correlated with SAT than with VAT.¹⁹ High leptin may indicate leptin resistance, which is predictive of type 2 diabetes.²¹ Another possibility is that in women, SAT is less likely to proliferate new cells (hyperplasia) and instead expands primarily by increasing adipocyte size (hypertrophy).²² Increased adipocyte size is associated with insulin resistance.^{23, 24} This may represent failure of SAT to expand sufficiently to store excess fat, leading to accumulation into VAT or other ectopic depots. However, a secondary analysis found that the associations of SAT with CVD risk factors in women were not materially different after adjusting for VAT volume.

The observation that both VAT and SAT attenuation, as indirect measures of fat quality, are associated with metabolic risk factors may relate to the fact that more negative fat attenuation represents more lipid-dense fat tissue, which in turn correlates with adipocyte size.²⁵ As noted above, larger adipocyte size may represent an inability to proliferate new adipocyte cells and is associated with insulin resistance.²⁴ The observation that the associations of fat quality with metabolic risk are not fully explained by fat volume, again suggests that SAT in women may have limited capacity for hyperplasia, leading to ectopic fat deposition.²⁶

An alternative hypothesis for the relevance of fat quality in predicting metabolic risk is that fat quality may be affected by vascularity of adipose tissue. Blood has higher HU attenuation than fat on CT.²⁷ Thus, lower HU attenuation of a fat depot may indicate relative dearth of vascularity. It is plausible that lack of vascularity could lead to hypoxia and higher inflammation, both of which may mediate pathogenic effects of adipose tissue.^{3, 28}

Implications

The results of the present study show that both VAT and SAT are associated with the development of metabolic risk independent of their contributions to overall adiposity. Our findings also demonstrate that fat attenuation is informative over and above fat volume alone in understanding metabolic risk associated with fat depots. Finally, our results suggest that

there may be important differences between men and women in how fat depots contribute to metabolic risk. Future research is needed to better understand the cellular and molecular mechanisms by which these unique depots confer risk.

Strengths and limitations

The large sample size is a strength of our study. Fat depots were precisely assessed with validated tools and strong inter-reader reliability. The data is prospective and allowed us to assess change over time. Metabolic risk factors were directly measured on site, which is more reliable than self-report. Because this is an observational study, we cannot infer causality between the measures of VAT and SAT and the metabolic outcomes. The Framingham cohort is primarily white, thus results may not be generalizable to other ethnicities. Finally, the numbers of some of the incident clinical risk factors were low. Our continuous analysis reinforces the association between increasing fat quantity and lower attenuation and change in CVD risk factors over time.

Conclusion

Both VAT and SAT volume are associated with incident metabolic risk factors after BMI adjustment, particularly among women. Fat attenuation, as an indirect measure of fat quality, provides additional information beyond fat volume. These findings suggest that both volume and quality of distinct fat depots contribute to an individual's metabolic risk, and that knowledge of the properties of fat depots has the potential to further our understanding of the heterogeneous metabolic risks conferred by obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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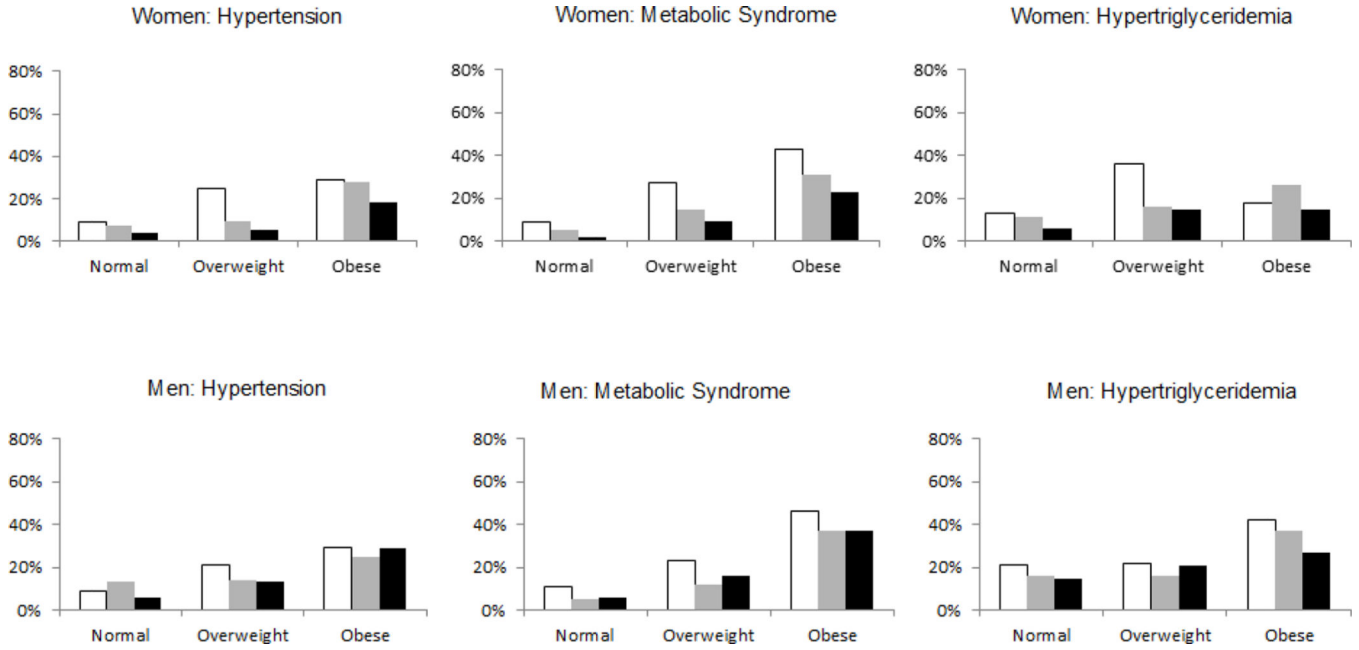


Figure 1. Sex-specific incidence of risk factors stratified by VAT attenuation tertiles within BMI Categories

Normal weight defined as BMI < 25 kg/m², overweight defined as BMI 25 to < 30 kg/m², obese defined as BMI ≥ 30 kg/m². VAT attenuation tertiles depicted as white bars (lowest tertile, i.e. most negative attenuation), gray bars (middle tertile) or black bars (highest tertile, i.e. least negative attenuation). Due to exclusion of individuals with the outcome present at baseline, the study populations differed for each outcome. For hypertension, the study populations consisted of 361, 171 and 116 women and 205, 370 and 153 men in the normal, overweight and obese categories, respectively. For metabolic syndrome, the study populations were 389, 162 and 89 women and 222, 348 and 82 men in each successive BMI category. For hypertriglyceridemia, the study populations were 370, 165 and 115 women, and 187, 271 and 113 men in each successive BMI category.

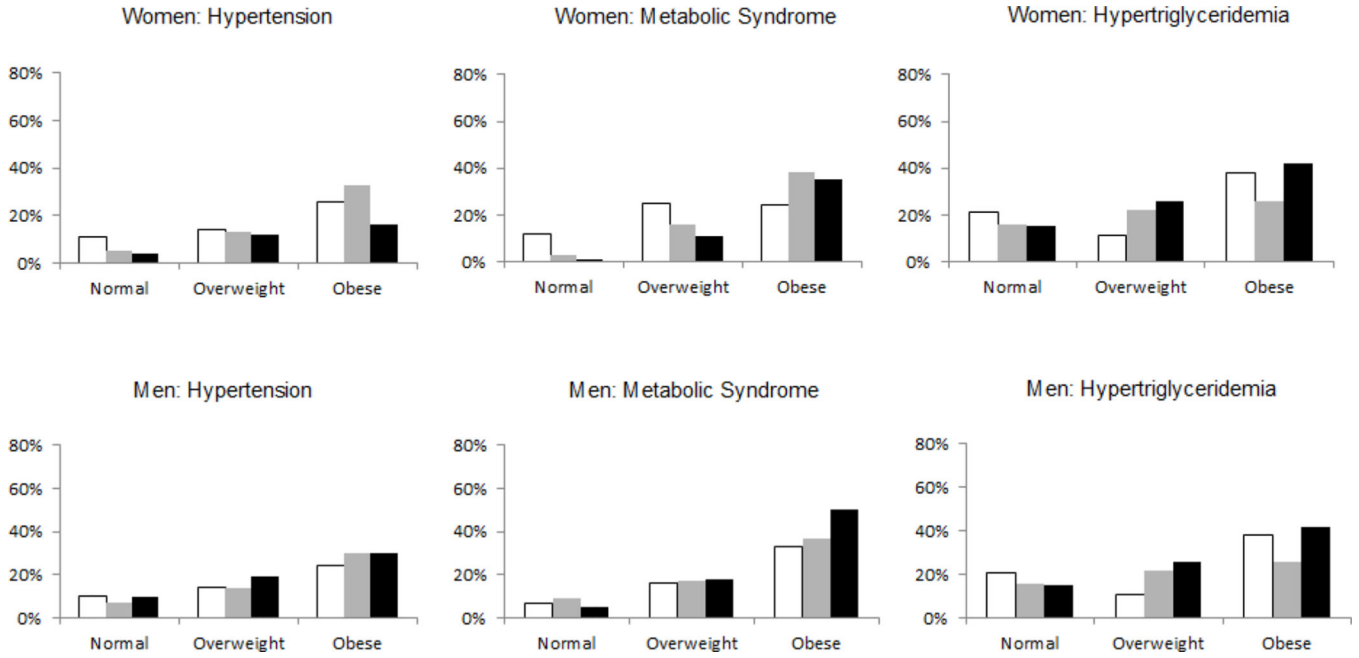


Figure 2. Sex-specific incidence of risk factors stratified by SAT attenuation tertiles within BMI Categories

Normal weight defined as BMI < 25 kg/m², overweight defined as BMI 25 to < 30 kg/m², obese defined as BMI ≥ 30 kg/m². SAT attenuation tertiles depicted as white bars (lowest tertile, i.e. most negative attenuation), gray bars (middle tertile) or black bars (highest tertile, i.e. least negative attenuation). Due to exclusion of individuals with the outcome present at baseline, the study populations differed for each outcome. For hypertension, the study populations consisted of 361, 171 and 116 women and 205, 370 and 153 men in the normal, overweight and obese categories, respectively. For metabolic syndrome, the study populations were 389, 162 and 89 women and 222, 348 and 82 men in each successive BMI category. For hypertriglyceridemia, the study populations were 370, 165 and 115 women, and 187, 271 and 113 men in each successive BMI category.

Table 1

Baseline Study Sample Characteristics. Continuous data shown are mean (SD) except for triglycerides (median with interquartile range); Fat volume and attenuation data are mean (SD) followed by median with interquartile range. Categorical data are shown as % (n).

	Women n=772	Men n = 958
Age (years)	46.0 (5.7)	44.1 (6.3)
Current Smoking (%)	12.7 (98)	14.3 (137)
Physical Activity Index	36.4 (5.9)	38.3 (9.1)
Moderate - Heavy Alcohol Use (%)*	14.5 (112)	15.7 (150)
Postmenopausal (%)	24.0 (185)	N/A
Hormone Replacement (%)	8.4 (65)	N/A
BMI (kg/m ²)	26.3 (5.8)	28.0 (4.4)
Normal Weight (BMI < 25 kg/m ²) (%)	51.3	24.1
Overweight (BMI 25 to < 30 kg/m ²) (%)	26.4	49.7
Obese (BMI ≥ 30 kg/m ²) (%)	22.3	26.2
Waist Circumference (cm)	90 (15)	99 (12)
Systolic Blood Pressure (mmHg)	117 (16)	121 (13)
Diastolic Blood Pressure (mmHg)	74 (9)	79 (9)
Fasting Glucose (mg/dl)	93 (16)	100 (21)
HDL Cholesterol (mg/dl)	63 (18)	47 (12)
Triglycerides (mg/dl)	81.0 (61.0,113.5)	112.0 (75.0,168.0)
Hypertension (%) [†]	15.7 (121)	24.0 (230)
Diabetes (%) ^{‡‡}	2.3 (18)	3.9 (37)
Low HDL Cholesterol (%) ^{††}	23.6 (182)	29.8 (285)
Hypertriglyceridemia (%) [‡]	15.8 (122)	40.3 (386)
Metabolic Syndrome (%) ^{**}	17.0 (131)	31.9 (305)
VAT Volume (cm ³)	1103 (715) 885 (537, 1493)	1977 (877) 1897 (1334, 2533)
SAT Volume (cm ³)	2954 (1548) 2627 (1828, 3893)	2566 (1227) 2334 (1745, 3162)
VAT Attenuation (HU)	-91.9 (4.3) -91.4 (-95.5, -88.5)	-95.5 (4.5) -96.4 (-98.8, -92.5)
SAT Attenuation (HU)	-101.9 (5.3) -103.2 (-105.4, -99.6)	-99.8 (4.6) -100.6 (-102.9, -98.2)

* Defined as > 14 drinks/week in men, > 7 drinks/week in women

[†] Defined as SBP ≥ 140 or DBP ≥ 90mm Hg or use of anti-hypertension medication

^{††} HDL < 40 mg/dL in men or < 50mg/dL in women

[‡] Defined as triglycerides ≥ 150mg/dL

^{‡‡} Defined as fasting glucose ≥ 126 mg/dL or use of anti-diabetes medication

** Metabolic Syndrome defined by modified ATP III criteria¹⁴

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Table 2 Sex-Specific Linear Regression Models predicting change (with 95% CI) in each outcome at follow-up per 500 cm³ increase in baseline fat volume[†]

	WOMEN				MEN				Sex Inter-action
	MV [‡]	P	MV + BMI	P	MV [‡]	P	MV + BMI	P	
SBP	N=698				N=848				
VAT	1.77 (1.04, 2.50)	<0.0001	0.86 (-0.31, 2.03)	0.15	1.02 (0.58, 1.47)	<0.0001	1.04 (0.40, 1.67)	0.0013	0.65
SAT	0.96 (0.65, 1.28)	<0.0001	1.22 (0.51, 1.92)	0.0008	0.35 (0.05, 0.66)	0.02	-0.17 (-0.74, 0.39)	0.55	0.13
DBP	N=696			N=848					
VAT	1.04 (0.56, 1.51)	<0.0001	0.77 (>-0.01, 1.54)	0.051	0.42 (0.10, 0.74)	0.01	0.44 (-0.01, 0.88)	0.06	0.06
SAT	0.55 (0.35, 0.76)	<0.0001	0.93 (0.46, 1.40)	0.0001	0.12 (-0.09, 0.34)	0.25	-0.13 (-0.53, 0.27)	0.53	0.02
Glucose	N=761				N=933				
VAT	2.34 (1.71, 2.97)	<0.0001	2.81 (1.78, 3.84)	<0.0001	1.19 (0.56, 1.82)	0.0002	0.87 (-0.02, 1.76)	0.06	0.06
SAT	0.71 (0.43, 1.00)	<0.0001	0.36 (-0.28, 1.01)	0.27	0.80 (0.38, 1.23)	0.0002	0.67 (-0.16, 1.50)	0.11	0.66
HDL	N=732				N=821				
VAT	-1.62 (-2.28, -0.97)	<0.0001	-1.86 (-2.98, -0.74)	0.001	-0.44 (-0.85, -0.03)	0.04	0.12 (-0.46, 0.70)	0.69	0.01
SAT	-0.60 (-0.89, -0.31)	<0.0001	-0.67 (-1.37, 0.03)	0.06	-0.39 (-0.66, -0.13)	0.004	0.01 (-0.51, 0.53)	0.97	0.54
Log Triglycerides	N=732				N=821				
VAT	0.05 (0.03, 0.07)	<0.0001	0.07 (0.03, 0.10)	0.0002	0.01 (-0.00, 0.03)	0.14	0.00 (-0.02, 0.03)	0.86	0.08
SAT	0.02 (0.01, 0.02)	0.0007	0.03 (<0.01, 0.05)	0.02	0.01 (-0.00, 0.02)	0.28	-0.01 (-0.03, 0.01)	0.28	0.44

[†] Estimates are change in the parameter (Exam 2 value - Exam 1 value) for a 500 cm³ increase in fat volume. Positive values indicate that larger values of SAT or VAT at Exam 1 are associated with increases in the parameter. Negative values indicate that larger values of SAT or VAT at Exam 1 are associated with decreases in the parameter at follow up.

[‡] MV model adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (Women only), and Hormone Replacement Therapy (Women only). Additional covariates included Exam 1 values of the parameter. SBP and DBP models excluded participants on hypertensive medications at baseline (and imputed +10/+5 if patient was on hypertension medications at Exam 2). Other models excluded participants on diabetes medications or lipid lowering medications (as appropriate)

Table 3 Sex-Specific Logistic Regression Models predicting incidence of each risk factor per 500cm³ increment in baseline fat volume[‡]

	WOMEN				MEN				Sex Inter-action	
	MV [‡]	P	MV + BMI	P	MV [‡]	P	MV + BMI	P	P	P
Hypertension					N=121/728					
VAT	1.24 (1.02, 1.51)	0.03	1.13 (0.83, 1.53)	0.44	1.28 (1.12, 1.47)	0.0003	1.29 (1.07, 1.56)	0.01	0.62	0.62
SAT	1.16 (1.06, 1.26)	0.001	1.38 (1.11, 1.71)	0.004	1.04 (0.95, 1.13)	0.40	0.80 (0.67, 0.95)	0.01	0.13	0.13
Diabetes					N=36/916					
VAT	1.46 (1.05, 2.02)	0.02	1.50 (0.88, 2.56)	0.14	1.34 (1.08, 1.65)	0.008	1.09 (0.83, 1.44)	0.52	0.85	0.85
SAT	1.12 (0.97, 1.29)	0.13	0.99 (0.73, 1.35)	0.97	1.19 (1.05, 1.36)	0.006	0.92 (0.72, 1.19)	0.53	0.46	0.46
Low HDL					N=36/671					
VAT	1.15 (0.85, 1.56)	0.36	1.07 (0.63, 1.81)	0.81	1.15 (0.93, 1.42)	0.19	0.99 (0.74, 1.33)	0.96	0.97	0.97
SAT	1.09 (0.95, 1.25)	0.24	1.17 (0.80, 1.72)	0.42	1.13 (0.99, 1.30)	0.06	1.03 (0.77, 1.38)	0.84	0.73	0.73
Hyper-triglyceridemia					N=125/570					
VAT	1.19 (1.01, 1.40)	0.04	1.36 (1.01, 1.84)	0.045	1.13 (0.99, 1.29)	0.06	1.07 (0.89, 1.29)	0.46	0.64	0.64
SAT	1.02 (0.95, 1.11)	0.59	0.92 (0.76, 1.10)	0.35	1.04 (0.95, 1.13)	0.41	0.87 (0.73, 1.03)	0.12	0.79	0.79
Metabolic Syndrome					N=108/651					
VAT	2.58 (2.05, 3.25)	<0.0001	2.50 (1.78, 3.52)	<0.0001	1.70 (1.45, 1.98)	<0.0001	1.31 (1.07, 1.60)	0.01	0.007	0.007
SAT	1.36 (1.25, 1.49)	<0.0001	1.08 (0.87, 1.33)	0.48	1.36 (1.23, 1.52)	<0.0001	0.91 (0.75, 1.11)	0.36	0.87	0.87

[‡] Estimates are odds ratios (95% CI) of the condition for a 500 cm³ increase in fat volume.

[‡] MV model adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (Women only), and Hormone Replacement Therapy (Women only). Diabetes models were additionally adjusted for fasting glucose (at baseline). Hypertension model was additionally adjusted for baseline SBP and baseline DBP. Low HDL models and Hypertriglyceridemia models were additionally adjusted for baseline HDL and baseline log triglycerides, respectively.

Table 4 Sex-Specific Linear Regression Models predicting change in each outcome between exams per 5 HU decrement baseline in fat attenuation[†]

	WOMEN				MEN				Sex Interaction
	MV [‡]	P	MV + Fat Volume	P	MV [‡]	P	MV + Fat Volume	P	
	N=698				N=848				
SBP									
VAT HU	1.49 (0.37, 2.60)	0.01	-0.61 (-2.11, 0.89)	0.43	1.68 (0.88, 2.48)	<0.0001	0.65 (-0.61, 1.92)	0.31	0.35
SAT HU	2.19 (1.35, 3.03)	<0.0001	1.23 (0.28, 2.19)	0.01	0.80 (0.04, 1.56)	0.04	0.43 (-0.51, 1.36)	0.37	0.07
DBP									
VAT HU	0.42 (-0.32, 1.16)	0.27	-1.15 (-2.13, -0.17)	0.02	0.76 (0.19, 1.34)	0.01	0.44 (-0.46, 1.33)	0.34	0.54
SAT HU	1.35 (0.80, 1.89)	<0.0001	0.83 (0.20, 1.46)	0.01	0.53 (-0.01, 1.07)	0.053	0.52 (-0.13, 1.18)	0.12	0.046
Glucose									
VAT HU	2.91 (1.90, 3.91)	<0.0001	0.65 (-0.73, 2.04)	0.36	2.23 (1.10, 3.37)	0.0001	1.40 (-0.44, 3.24)	0.14	0.44
SAT HU	1.34 (0.56, 2.12)	0.0008	0.48 (-0.42, 1.37)	0.30	1.69 (0.56, 2.82)	0.004	0.66 (-0.75, 2.07)	0.36	0.70
HDL									
VAT HU	-2.19 (-3.26, -1.13)	<0.0001	-0.73 (-2.19, 0.74)	0.33	-0.44 (-1.23, 0.35)	0.27	0.44 (-0.75, 1.64)	0.47	0.04
SAT HU	-2.68 (-3.46, -1.89)	<0.0001	-2.46 (-3.37, -1.55)	<0.0001	-0.66 (-1.39, 0.06)	0.07	-0.09 (-0.97, 0.79)	0.84	0.0008
Log Triglycerides									
VAT HU	0.08 (0.05, 0.12)	<0.0001	0.06 (0.02, 0.11)	0.005	0.01 (-0.02, 0.04)	0.64	-0.02 (-0.07, 0.03)	0.37	0.01
SAT HU	0.06 (0.03, 0.08)	<0.0001	0.05 (0.02, 0.07)	0.002	0.01 (-0.02, 0.04)	0.65	> -0.01 (-0.04, 0.03)	0.85	0.06

[†] Estimates are change in the parameter (exam 2 value - exam 1 value) for a 5 unit decrease in HU (more negative).

[‡] MV model adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (Women only), and Hormone Replacement Therapy (Women only). Additional covariates included Exam 1 values of the parameter. SBP and DBP models excluded participants on hypertensive medications at baseline (and imputed +10/+5 if patient was on hypertension medications at Exam 2). Other models excluded participants on diabetes medications or lipid lowering medications (as appropriate).

Table 5

Sex-Specific Logistic Regression Models predicting incidence of each risk factor per 5 HU decrement in baseline fat attenuation[†]

	WOMEN				MEN				Sex Inter-action
	MV [‡]	P	MV + Fat Volume	P	MV [‡]	P	MV + Fat Volume	P	
Hypertension									
VAT HU	N=75/648 1.48 (1.05, 2.08)	0.02	1.31 (0.81, 2.10)	0.27	N=121/728 1.34 (1.03, 1.74)	0.03	0.81 (0.53, 1.23)	0.31	0.77
SAT HU	1.29 (0.94, 1.77)	0.12	1.06 (0.76, 1.50)	0.72	1.02 (0.79, 1.31)	0.91	0.94 (0.70, 1.27)	0.69	0.40
Diabetes									
VAT HU	N=20/753 1.40 (0.75, 2.64)	0.29	0.59 (0.21, 1.64)	0.31	N=36/916 1.54 (0.92, 2.59)	0.10	0.92 (0.45, 1.87)	0.81	0.80
SAT HU	1.38 (0.67, 2.85)	0.38	1.19 (0.55, 2.58)	0.66	1.24 (0.72, 2.13)	0.44	0.84 (0.47, 1.51)	0.57	0.84
Low HDL									
VAT HU	N=19/590 1.26 (0.71, 2.21)	0.43	1.08 (0.45, 2.60)	0.86	N=36/671 0.88 (0.59, 1.32)	0.54	0.42 (0.22, 0.81)	0.01	0.34
SAT HU	1.24 (0.72, 2.14)	0.44	1.10 (0.60, 2.00)	0.75	0.83 (0.58, 1.19)	0.31	0.57 (0.37, 0.89)	0.01	0.16
Hypertriglyceridemia									
VAT HU	N=96/650 1.38 (1.04, 1.85)	0.03	1.27 (0.83, 1.94)	0.27	N=125/570 1.05 (0.81, 1.35)	0.72	0.74 (0.51, 1.09)	0.13	0.22
SAT HU	1.42 (1.05, 1.95)	0.02	1.48 (1.06, 2.07)	0.02	0.91 (0.72, 1.15)	0.42	0.80 (0.61, 1.06)	0.13	0.03
Metabolic Syndrome									
VAT HU	N=78/639 3.07 (2.20, 4.28)	<0.0001	1.20 (0.74, 1.95)	0.47	N=108/651 1.87 (1.44, 2.44)	<0.0001	0.82 (0.54, 1.25)	0.36	0.04
SAT HU	2.46 (1.72, 3.52)	<0.0001	1.68 (1.15, 2.47)	0.01	1.25 (0.98, 1.59)	0.07	0.76 (0.57, 1.01)	0.06	0.003

[†] Estimates are odds ratios (95% CI) for the condition for a 5 unit decrease in HU.

[‡] MV model adjusted for age, physical activity, alcohol intake, smoking status, menopausal status (Women only), and Hormone Replacement Therapy (Women only). Diabetes/IFG models were additionally adjusted for fasting glucose (at baseline). Hypertension model was additionally adjusted for baseline SBP and baseline DBP. Low HDL models and Hypertriglyceridemia models were additionally adjusted for baseline HDL and baseline triglycerides, respectively.