Depressive symptoms are associated with visceral adiposity in a community-based sample of middle-aged women and men

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Depressive symptoms are associated with visceral adiposity in a community-based sample of middle-aged women and men

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Abstract

To examine the relation between measures of adiposity and depressive symptoms in a large well characterized community-based sample, we examined the relations of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) to depressive symptoms in 1581 women (mean age 52.2 years) and 1718 men (mean age 49.8 years) in the Framingham Heart Study. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) scale. Regression models were created to examine the association between each fat depot (exposure) and depressive symptoms (outcome). Sex specific models were adjusted for age, body mass index, smoking, alcohol consumption, diabetes, hypertension, total and HDL cholesterol, lipid lowering treatment, CVD, menopause, C-reactive protein, and physical activity. Mean CES-D scores were 6.8 and 5.6 in women and men. High levels of depressive symptoms were present in 22.5% of women and 12.3% of men. In women, one standard deviation increase in VAT was associated with a 1.3 point higher CES-D score after adjusting for age and BMI ($p<0.01$) and remained significant in the fully adjusted model ($p=0.03$). The odds ratio of depressive symptoms per 1 standard deviation increase in VAT in women was 1.33 ($p=0.015$); results were attenuated in fully adjusted models (OR 1.29, $p=0.055$). In men, the association between VAT and CES-D score and depressive symptoms was not significant. SAT was not associated with CES-D score or depressive symptoms. This study supports an association between VAT and depressive symptoms in women. Further work is needed to uncover the complex biologic mechanisms mediating the association.

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Introduction

Depressive symptoms are common, often occur in adolescence or early adulthood, and are associated with an increased risk for type 2 diabetes, cardiovascular disease (CVD) events and all-cause mortality.(1-3) However, the underlying biologic mechanisms mediating these associations remain under investigation. Adiposity may be one potential pathway through which depressive symptoms contribute to diabetes and CVD risk. The relation between depression and adiposity appears to be bidirectional (4) and may be modified by gender and fat distribution. Depression is associated with greater adiposity in women (5) and depressive symptoms increase risk for abdominal obesity in community-dwelling elders.(6) Conversely, obesity, particularly visceral adiposity, is associated with increased risk of new depressive symptoms in older men but not older women.(7) Small studies, mostly in women, demonstrate that depressed patients have higher amounts of visceral adipose tissue (VAT) compared with non-depressed individuals.(8) In a study of middle-aged women (mean age 50 years, over 70% overweight or obese), VAT, but not subcutaneous adipose tissue (SAT) or waist circumference, was related to depressive symptoms.(9) These data suggest a complex relationship between adiposity and depressive symptoms with additional research needed in large community-based samples that include younger and middle-aged men and women with assessment of overall obesity as well as measurement of specific fat depots.

We sought to examine the relation between measures of adiposity and depressive symptoms in a large well characterized community-based sample of both men and women. Our sample included men and women across adulthood (age 31 to 83 years) and across a wide range of body mass index levels (15.8 to 55.9 kg/m^2). We hypothesized that individuals with greater amounts of VAT and SAT would be at increased risk for the presence of high levels of depressive symptoms even after adjustment for overall obesity and other important potential confounding factors. Further, we hypothesized that relationships would be stronger for VAT, a fat depot strongly associated with adverse metabolic risk(10) and increased inflammation and oxidative stress(11), pathways that may provide an important link between adiposity and depressive symptoms.

Methods and Procedures

Study Sample

Participants for this study were drawn from the Framingham Heart Study (FHS) Multi-detector Computed Tomography (MDCT) Study, a substudy of the community-based Framingham Offspring and Third Generation (Gen 3) cohorts.(10) The FHS was initiated in 1948 to study determinants of cardiovascular disease and other health conditions. Beginning in 1971 the Offspring of the Original Cohort members and Offspring spouses were enrolled (n=5124) and from 2002 to 2005 Gen 3 participants with at least one parent in the Offspring cohort were enrolled (n=4095). Details of study design of Offspring and Gen 3 cohorts have been previously reported.(12;13)

From 2002 to 2005, 3529 participants (2111 Gen 3 and 1418 Offspring participants) underwent MDCT assessment for coronary and aortic calcification and 3370 had measures of both SAT and VAT.(10) Among this group, 23 did not undergo assessment of depressive symptoms, 30 had incomplete depression information (missing CES-D survey score or information on antidepressant medication use) and 18 did not have complete risk factor information, leaving 3299 for this study. The Institutional Review Board at Boston University Medical Center approved this study and all participants provided written informed consent.

Measures of VAT and SAT

Eight-slice multi-detector computed tomography scanning of the abdomen was obtained as previously described (LightSpeed Ultra, General Electric, Milwaukee, WI).(14) We measured SAT and VAT volumes (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA), which required the reader to manually trace the abdominal muscular wall, which separates the subcutaneous and visceral fat compartments. Applying an image display window of -195 to -45 Hounsfield Units (HU) results in semi-automatic quantification of SAT and VAT volumes. Inter-class correlations for inter-reader comparisons were 0.997 for SAT and 0.992 for VAT; correlations for intra-reader comparisons were similarly high.(14)

Measure of Depressive Symptoms

Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale developed and validated by the Center for Epidemiologic Studies, National Institute of Mental Health. Trained technicians administered the CES-D to Gen 3 participants attending Gen 3 examination 1 (2002-2005) and to Offspring participants attending Offspring examination 7 (1998-2001). The mean time between CES-D assessment and MDCT assessment of SAT and VAT was 0.2 years (0.38 SD) in Gen 3 participants and 4.2 years (0.95 SD) in Offspring participants. Participants were asked to provide responses to the 20 items that corresponded to how they were feeling during the past week with response choice options of: 0=rarely or none of the time (< 1day), 1=some or a little of the time (1-2 days), 2=occasionally or a moderate amount of time (3-4 days), and 3=most or all of the time (5 to 7 days). The CES-D was then scored by summing the coded response values for all 20 items with the total scale score range of 0 to 60. A score of 16 or higher was designated as consistent with the presence of depressive symptoms in accordance with previous recommendations.(15) If a participant had missing responses for more than 5 items, then the CES-D score was set to missing (n=29) and the participant was excluded from this study whereas if one to five items was missing (n=211) then the non-missing scale items were totaled and the total score divided by the number of non-missing items and this value was then multipled by 20. In addition, participants were queried by trained physicians regarding use of anti-depressant medications. At Gen 3 exam 1, participants were asked to bring all medication bottles to the research examination to further verify self-reported medication use. If a participant was missing antidepressant use status (n=1), the participant was excluded.

Covariates and potential confounders

Covariates were measured at the closest examination (Gen 3 exam 1 and Offspring exam 7 respectively). Height, weight, and waist circumference were directly measured by trained technicians and body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. A technician-administered physical activity questionnaire was used to calculate a physical activity index score based on the average number of hours daily of sleep and sedentary, slight, moderate and high activity the participant reported. Medication use, smoking status and alcohol consumption were recorded as part of the standard physician-administered medical history interview. Current smoking was defined as smoking at least one cigarette per day over the year preceding the exam. Moderate alcohol intake was defined as greater than 14 drinks per week in men and greater than 7 drinks per week in women. Women were additionally queried about menopausal status and postmenopausal hormone use with a standard series of questions. Hypertension was defined using physician obtained blood pressure readings as ≥140/90 mm Hg or use of anti-hypertensive medications. Fasting morning blood samples were used to measure fasting plasma glucose, total and high density lipoprotein (HDL) cholesterol, and C-reactive protein. Diabetes was defined as a fasting glucose ≥126 mg/dL or use of insulin or oral hypoglycemic agents. Prevalent CVD was defined using previously published criteria and

included coronary heart disease, congestive heart failure, stroke or transient ischemic attack and intermittent claudication.(16)

Statistical methods

The relationship between adiposity and each of the following two depressive symptoms outcomes was examined: a continuous total CES-D score and high levels of depressive symptoms (a dichotomous CES-D score ≥16 and/or use of anti-depressant medications). Specifically, the cross-sectional relation between SAT and VAT (modeled as the exposure) and depressive symptoms (modeled as the outcomes) was assessed using multivariable linear (for CES-D score) and logistic regression (for presence of high levels of depressive symptoms) with separate models for SAT and VAT. All models were sex specific due to the presence of a significant VAT x sex interaction (p=0.001) in the initial model adjusted for age, sex, and BMI with CES-D score as the dependent variable. We did not find any significant VAT x cohort interaction (Offspring vs Gen 3) or SAT x cohort interaction with CES-D score or high levels of depressive symptoms (all p values > 0.10) therefore we did not run separate models by cohort. The effects of adiposity on depressive symptoms are presented as the mean change in CES-D score and change in odds of high levels of depressive symptoms per 1 standard deviation increment increase in SAT or VAT. Because anti-depressant medication use may affect the CES-D score, in the linear regression we first imputed the CES-D score for participants on antidepressant medications following a similar algorithm previously used by Framingham investigators to impute blood pressure readings for individuals on anti-hypertensive agents.(17) Specifically, we imputed CES-D scores for each participant with self-reported anti-depressant use by replacing the participant's observed CES-D score with the mean CES-D score of all participants reporting anti-depressant medication use having the same or higher score. Thus, with the imputation procedure it was assumed that individuals on anti-depressants with the lowest CES-D scores had a larger antidepressant effect than individuals with higher CES-D scores. Initial linear and logistic models were adjusted for age and BMI and then full multivariable models were further adjusted for smoking status, alcohol consumption, diabetes, prevalent CVD, hypertension, total cholesterol, HDL cholesterol, lipid lowering treatment, and menopausal status. In secondary analyses we further adjusted for C-reactive protein and physical activity. All statistical analyses were performed using SAS version 9.1.

Results

The study sample comprised 1581 women (mean age 52.2 years) and 1718 men (mean age 49.8 years) with mean BMI in the overweight category and characteristics typical of a community-based sample (Table 1). As expected, the mean CES-D score was higher in women than men (imputed score 6.8 vs. 5.6; raw score 3.5 vs 2.6) as was the prevalence of CES-D score ≥ 16 (11.8% vs. 7.3%) and use of anti-depressant medications (15.0% vs. 6.9%). Thus, the presence of high levels of depressive symptoms (CES-D ≥16 and/or antidepressant medication use) was higher in women than men (22.5% vs. 12.3%).

Estimates of the increment in mean CES-D score per 1 standard deviation increase in VAT or SAT for each linear regression model are presented in Table 2. In women, one standard deviation increase in VAT was associated with an average increase in CES-D of 1.3 after adjusting for age and BMI (p<0.01). The estimate remained significant and only slightly attenuated in the fully adjusted model (1.1 point mean higher CES-D score per standard deviation of VAT) and was not further attenuated after adjustment for C-reactive protein or the physical activity index. No association between VAT and CES-D score was seen in men. There was no association between SAT and CES-D score in women or men. We repeated the analysis using raw CES-D scores without imputation. The relation between VAT and depressive symptoms in women persisted but with an attenuation in the effect. In women,

one standard deviation increase in VAT was associated with an average increase in CES-D score of 1.1 after adjusting for age, BMI and antidepressant medication use (p=0.005) and an average increase in CES-D score of 0.8 in fully adjusted models (p=0.05).

Women had 1.33 times the odds of high levels of depressive symptoms per one standard deviation increase in VAT after adjusting for age and BMI (p<0.015) (Table 3). The increased odds of high levels of depressive symptoms associated with VAT were attenuated in the covariate adjusted model (OR 1.27, p=0.055) and in the model adjusted for C-reactive protein and physical activity (OR 1.29, p=0.055). In men, in the age and BMI adjusted model, the odds of high levels of depressive symptoms per standard deviation increase in VAT was 1.24 (p=0.052) but the association was no longer significant in the fully adjusted model (odds 1.14, p=0.27). SAT was not associated with increased odds of high levels of depressive symptoms in women or men (Table 3).

Discussion

Principal findings

Our large community-based study of middle-aged individuals demonstrates a cross-sectional relation between VAT and depressive symptoms in women but in our sample there was not an association in men. The relation persisted after adjustment for overall obesity (body mass index) and important confounders such as menopausal status and markers of inflammation (C-reactive protein) which may represent potential pathways linking adiposity and depression. Adiposity, particularly VAT, and depressive symptoms are both associated with increased inflammation. (18) No relation between SAT and depressive symptoms was observed in women or men. The heterogeneity of the associations in the two fat depots may highlight the differences in metabolic activity within each fat depot. Specifically, VAT is a unique pathogenic fat depot that consists of metabolically active adipose tissue.(19) In contrast, SAT may serve as an ectopic fat reservoir and as such has been considered to be a potential protective fat depot in animal studies (20;21) although the literature in humans is less convincing.(21) Our study makes an important contribution to the literature by investigating a large community-based sample of both men and women across adulthood including both pre- and postmenopausal women and across a wide range of BMI levels using volumetric measures of VAT and objective measures of overall obesity and potential confounders.

In the context of the current literature

Much of the existing literature has focused on anthropometric measurements and correlations with depressive indices. A recent meta-analysis demonstrated a bidirectional relation between obesity and depression such that obese persons (BMI ≥30 kg/m^2) were at increased risk of developing depression over time and depressed individuals were at increased risk of becoming obese.(4) Further, there appeared to be a dose-response relation as associations were stronger in obese compared to overweight individuals. In a large population-based sample of US women, BMI was associated with moderate-to-severe depressive symptoms and major depression.(22) In that report abdominal obesity, measured by waist circumference, was also positively associated with depressive symptoms independent of BMI. A second large community-based study (the second Health Survey of North-Trondelag County Norway, the HUNT-2 Study) also reported an association between abdominal obesity, defined with waist-hip ratio, and depression in both women and men. (23) While additional studies have also found a relation between depressive symptoms and waist circumference or waist-hip ratio in women (24), other studies have not found an association between abdominal obesity and depression.(25)

Few studies have examined the association between VAT and depressive symptoms. Consistent with findings from our study, depressive symptoms were strongly associated with VAT in a study of mostly overweight and obese peri- and postmenopausal women (9) and in a small study of overweight premenopausal women.(26) Interestingly, in a study of older high functioning adults aged 70 to 79 at baseline, VAT was predictive of the onset of depressive symptoms in men but not in women in contrast to our findings (7) whereas the presence of depressive symptoms were associated with an increase in VAT over 5 years independent of BMI.(6) Our study extends the previous reports in several important ways. First, we included a large community-based sample of both men and women with ages spanning early and mid-adulthood. Our sample was well characterized with respect to both directly measured anthropometry assessment as well as important potential confounding factors. Finally, we obtained volumetric measures of VAT. The association of VAT and depressive symptoms in women in our sample was present even after adjustment for BMI, covariates, measures of inflammation and physical activity.

Potential Mechanisms

The biologic mechanisms mediating the obesity-depressive symptoms relation remain poorly understood, however several potential mechanisms have been proposed including inflammation, hypothalamic-pituitary-adrenal axis (HPA) dysregulation and hypercortisolemia, and hormonal milieu. In addition, physical activity is an important causal factor for obesity (27) and is known to improve depressive symptoms.(28) While it is well known that excess adiposity is associated with increased inflammation, VAT is associated with increased inflammation even after accounting for BMI and waist circumference (16) suggesting a unique and important contribution of VAT to the inflammatory state. Inflammation in turn has been associated with depression and depressive symptoms in both healthy adults(29) and individuals with coronary syndromes(30). In the Study of Women's Health Across the Nation, higher C-reactive protein levels were associated with increased depressive symptoms and the association appeared to be bidirectional.(18) Similar findings were noted in a study of older adults, such that depressed mood was causing and/or caused by increased inflammation. (31) Thus, inflammation appears to play an important role in both adiposity and depressive symptoms and may be one mediator of the association between the two conditions. Similarly the transition to menopause and changes in the hormonal milieu in postmenopausal women have been associated with both changes in fat distribution(32) and increased depressive symptoms. (33) Menopause is significantly associated with VAT independent of aging and the effect appears to be mediated through sex hormone levels (higher bioavailable testosterone or lower sex hormone binding globulin) independent of total body adiposity.(32) Women with abdominal obesity have both central and peripheral alterations in the HPA axis(34) and HPA dysregulation has been linked to depression. Hence, there are likely to be multiple biologic mechanisms linking adiposity and depressive symptoms some of which may play a more important role in women than men. Our future work will focus on repeat assessment of measures of depressive symptoms and SAT and VAT which will allow us to examine the bi-directionality of the relation as well to examine whether inflammation and reproductive status are related to changes in fat distribution and depressive symptoms.

Limitations

Our study has some limitations that merit comment. First, our sample was white of European ancestry and thus findings cannot be generalized to other race/ethnicities. In at least one study, no relation was identified between depressive symptoms and visceral fat accumulation in older black women.(6) Second, the CES-D was used to detect depressive symptoms rather than clinical diagnostic criteria. Although the CES-D has been validated in psychiatric and community-based samples and is predictive of mortality and CVD events in

national surveys and longitudinal cohort studies(1), it is possible that relations with visceral fat would differ if a clinically diagnosed ascertainment was evaluated. In a meta-analysis of obesity defined by BMI category the association was stronger in individuals with a clinical diagnosis of depressive disorder than in those with depressive symptoms.(4) While we included antidepressant medication usage in our definitions of depressive symptoms, we cannot assess the impact of specific classes of anti-depressant medications on weight gain and adiposity. We did not assess diet which may be an important confounder in the adiposity-depressive symptoms relation. A recent report demonstrated elevated CES-D scores were associated with poorer-quality diet.(24) Physical activity improves both mood and adiposity and may provide an important link between the two conditions. Finally our study is cross-sectional and cannot infer causality. Further, the time between the CES-D measurement and MDCT assessment for SAT and VAT was 4.2 years in the Offspring cohort. However, the relationships between depressive symptoms and fat are similar to the findings we present in the manuscript when CES-D is modeled as the exposure variable with SAT and VAT modeled as the outcome variable. No relation between depressive symptoms (defined as a continuous score or the presence of high levels of depressive symptoms) and SAT was observed in women or men. In our sample, there was no association between depressive symptoms and VAT in men. However, in women one standard deviation increase in total CES-D score was associated with 28 cm^3 higher VAT (p=0.01 in the fully adjusted model) and the presence of high depressive symptoms was associated with 55 cm^3 higher VAT (p=0.07 in the fully adjusted model); results not previously presented.

Conclusions

Our community-based study results suggest a significant relation between VAT and depressive symptoms in middle-aged women that is independent of overall obesity and important confounders. Depressive symptoms and obesity are both common conditions with significant adverse effects on health that may be greater when the two conditions occur together. Further work is warranted to determine if VAT, a metabolically active adipose tissue depot, mediates the association between depressive symptoms and risk for CVD and type 2 diabetes and to develop effective prevention and intervention strategies to ameliorate these two common debilitating conditions.

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Table 1

Characteristics of the Study Sample at Assessment of Depressive Symptoms

Mean (SD) or % (N)	Women N=1581		Men N=1718	
Characteristics	**Mean or %**	**SD or N**	**Mean or %**	**SD or N**
Age, years	52.2	9.9	49.8	10.7
Education, < high school, %	1.0	15	1.9	30
Education, high school graduate, %	56.3	815	46.3	735
Education, > high school, %	42.6	616	51.9	824
Body mass index, kg/m2	27.0	5.8	28.4	4.5
Waist circumference, cm	93	16	101	12
Current smoking, %	12.4	196	13.4	230
Moderate alcohol intake, %	14.8	234	16.2	279
Menopausal status, %	50.5	798	NA	NA
Diabetes, %	5.4	86	7.4	127
Hypertension, %	26.7	422	32.0	549
Total/HDL cholesterol ratio	3.5	1.1	4.5	1.4
Lipid lowering treatment, %	10.6	167	17.8	305
Prevalent CVD, %	4.2	67	7.9	135
C-reactive protein[a], mg/L	1.69	0.65, 4.27	1.21	0.57, 2.70
Physical activity index	36.7	5.7	38.3	8.9
Exposures				
SAT, cm3	3135	1510	2633	1201
VAT, cm3	1359	834	2241	1022
Outcomes				
Raw CES-D score	3.5	5.2	2.6	5.1
Imputed CES-D score	6.8	7.6	5.6	6.2
Raw CES-D ≥16 and/or antidepressant medication use, %	22.5	356	12.3	211
Components of outcomes				
Raw CES-D ≥16, %	11.8	187	7.3	125
Antidepressant medication use, %	15.0	237	6.9	119

Moderate alcohol intake defined as > 14 drinks/week in men and > 7 drinks/week in women

CES-D= Center for Epidemiologic Studies Depression
CVD=cardiovascular disease
HDL= high density lipoprotein
SD=standard deviation
SAT= subcutaneous adipose tissue
VAT= visceral adipose tissue

[a] Median, 25th, 75th percentile provided

Table 2

Association between VAT and SAT and Total Imputed CES-D score: Results of Linear regression analyses

	Women			Men		
VAT*	**Increment in CES-D per 1 SD VAT**	**95 % CI**	**P value**	**Increment in CES-D per 1 SD VAT**	**95 % CI**	**P value**
Model 1: Age, BMI	1.3	0.5, 2.2	<0.01	0.2	-0.3, 0.7	0.40
Model 1: + covariates	1.1	0.2, 2.1	0.01	0.1	-0.45, 0.6	0.81
Model 1: +covariates, CRP, physical activity	1.1	0.1, 2.0	0.03	-0.1	-0.6, 0.5	0.85
SAT	**Increment in CES-D per 1 SD SAT**	**95 % CI**	**P value**	**Increment in CES-D per 1 SD SAT**	**95 % CI**	**P value**
Model 1: Age, BMI	-0.2	-1.0, 0.6	0.60	0.3	-0.4, 0.9	0.43
Model 1: + covariates	-0.2	-1.0, 0.7	0.71	0.4	-0.3, 1.0	0.28
Model 1: +covariates, CRP, physical activity	-0.2	-1.1, 0.6	0.61	0.2	-0.5, 0.9	0.52

*VAT x sex interaction p=0.001 in model adjusted for age, sex and BMI, thus all models are sex specific.

Covariates: smoking status, alcohol intake, diabetes mellitus, hypertension, total cholesterol, HDL cholesterol, lipid lowering treatment, prevalent cardiovascular disease, and in women menopausal status

BMI=body mass index
CI=confidence interval
CRP=C-reactive protein
SAT subcutaneous adipose tissue
VAT= visceral adipose tissue
SD=standard deviation

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Table 3

Association between VAT and SAT and High Levels of Depressive Symptoms (CES-D score ≥16 and/or antidepressant medication use): Results of Logistic regression analyses

	Women			Men		
VAT	**Odds per 1 SD VAT**	**95 % CI**	**P value**	**Odds per 1 SD VAT**	**95 % CI**	**P value**
Model 1: Age, BMI	1.33	1.06, 1.68	0.015	1.24	1.00, 1.54	0.052
Model 1: + covariates	1.27	1.00, 1.63	0.055	1.17	0.93, 1.46	0.18
Model 1: +covariates, CRP, physical activity	1.29	1.00, 1.66	0.055	1.14	0.90, 1.44	0.27
SAT	**Odds per 1 SD SAT**	**95 % CI**	**P value**	**Odds per 1 SD SAT**	**95 % CI**	**P value**
Model 1:Age, BMI	1.04	0.84, 1.29	0.71	1.07	0.81, 1.42	0.62
Model 1: + covariates	1.05	0.85, 1.32	0.64	1.13	0.85, 1.51	0.39
Model 1: +covariates, CRP, physical activity	1.04	0.82, 1.31	0.74	1.08	0.81, 1.44	0.61

Covariates: smoking status, alcohol intake, diabetes mellitus, hypertension, total cholesterol, HDL cholesterol, lipid lowering treatment, prevalent cardiovascular disease, and in women menopausal status

BMI=body mass index
CI=confidence interval
CRP=C-reactive protein
SAT subcutaneous adipose tissue
VAT= visceral adipose tissue
SD=standard deviation