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Difference by sex but not by race/ethnicity in the visceral adipose tissue-depressive symptoms association: The Multi-Ethnic Study of Atherosclerosis

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Summary

Background—Prior studies have investigated the association of clinical depression and depressive symptoms with body weight (i.e. body mass index (BMI) and waist circumference), but few have examined the association between depressive symptoms and intra-abdominal fat. Of these a limited number assessed the relationship in a multi-racial/ethnic population.

Methods—Using data on 1017 men and women (45–84 years) from the Multi-Ethnic Study of Atherosclerosis (MESA) Body Composition, Inflammation and Cardiovascular Disease Study, we examined the cross-sectional association between elevated depressive symptoms (EDS) and CT-measured visceral fat mass at L2–L5 with multivariable linear regression models. EDS were defined as a Center for Epidemiological Studies Depression score ≥ 16 and/or anti-depressant use. Covariates included socio-demographics, inflammatory markers, health behaviors, comorbidities, and body mass index (BMI). Race/ethnicity (Whites [referent group], Chinese, Blacks and Hispanics) and sex were also assessed as potential modifiers.

Results—The association between depressive symptoms and visceral fat differed significantly by sex ($p = 0.007$), but not by race/ethnicity. Among men, compared to participants without EDS, those with EDS had greater visceral adiposity adjusted for BMI and age (difference = 122.5 cm^2 , 95% CI = 34.3, 210.7, $p = 0.007$). Estimates were attenuated but remained significant after further adjustment by socio-demographics, inflammatory markers, health behaviors and co-morbidities (difference = 94.7 cm^2 , 95% CI = 10.5, 178.9, $p = 0.028$). Among women, EDS was not significantly related to visceral adiposity in the fully adjusted model.

Conclusions—Sex, but not race/ethnicity, was found to modify the relationship between EDS and visceral fat mass. Among men, a significant positive association was found between depressive symptoms and visceral adiposity. No significant relationship was found among women.

Keywords

Elevated depressive symptoms; Visceral adipose tissue; Visceral fat mass; Sex; Race/ethnicity; Antidepressant use

1. Introduction

The relationship between clinical depression or depressive symptoms and anthropometric measures of obesity has been mixed, although a recent meta-analysis supported a positive bi-directional association (Luppino et al., 2010). Inability to distinguish subcutaneous and visceral adipose tissue (SAT and VAT, respectively) using measures such as body mass index (BMI) and waist circumference may explain some of the discrepancies. Previous studies have shown a significant positive association between depressive symptoms and VAT, but not SAT, particularly among women (Thakore et al., 1997; Everson-Rose et al., 2009; Ludescher et al., 2011; Murabito et al., 2013). Few studies have reported on the association between depressive symptoms and intra-abdominal fat (Kahl et al., 2005; Lee et al., 2005; Weber-Hamann et al., 2006; Vogelzangs et al., 2008; Everson-Rose et al., 2009; Gregersen et al., 2011; Murabito et al., 2013), although a positive bidirectional relationship has been suggested among an elderly population (Vogelzangs et al., 2008, 2010).

A potential biological pathway through which depression might lead to abdominal obesity is neuroendocrine disturbances in the hypothalamic-pituitary-adrenal (HPA) axis (Chrousos and Gold, 1992; Deuschle et al., 1998; Bjorntorp and Rosmond, 2000; Weber-Hamann et al., 2002; Ludescher et al., 2008). This dysfunction is manifested as abnormally high levels of cortisol secretion, or altered ‘cortisol patterning’ (Musselman et al., 1998). Elevated cortisol contributes to the accumulation of VAT (Bjorntorp, 2001), an important predictor of type 2 diabetes and cardiovascular disease (Ohlson et al., 1985; Rexrode et al., 1998), possibly due to the high density of glucocorticoid receptors on VAT compared to SAT (Bronnegard et al., 1990; Pederson et al., 1994). Depression has been associated with increased VAT and adrenal gland volume, a marker of long-term stress, among women. (Ludescher et al., 2008). Conversely, greater VAT may lead to an increase in depressive symptoms. Adipose tissue, particularly VAT, secretes cytokines and inflammatory markers (e.g. interleukin-6 [IL-6], C-reactive protein [CRP], interleukin-1, interleukin-2) that may induce mood disturbance (Kent et al., 1992; Capuron et al., 2001; Musselman et al., 2001; Dantzer and Kelley, 2007; Gimeno et al., 2009a,b; Matthews et al., 2010). This is supported by studies demonstrating

an increase in depression or depressive symptoms associated with cytokines such as interferon-alpha (IFN- α) used to treat viral infections or malignant disorders (Musselman et al., 2001; Scheibel et al., 2004; Ehret and Sobieraj, 2014). Administration of antidepressants prior to IFN- α treatment has been shown to mitigate these symptoms (Musselman et al., 2001; Ehret and Sobieraj, 2014).

Studies have investigated differences in the depressive symptoms-VAT relationship by sex (Vogelzangs et al., 2008, 2010; Murabito et al., 2013). Murabito et al. (2013) found greater VAT among women with versus without elevated depressive symptoms (EDS). In a longitudinal assessment, Vogelzangs et al. (2008) found baseline EDS associated with an increase in VAT among men and White women, but an inverse relationship among Black women. Only the association among White men, however, was significant (Vogelzangs et al., 2008). While assessing VAT as a predictor of EDS, significance was found only among men in this same cohort (Vogelzangs et al., 2010). Murabito et al. (2013), however, did not support this finding.

The reasons for the sex difference in the association between depression and VAT are still unclear; however, there are hypothesized contributors to this disparity. The association of depression and stress to greater HPA dysregulation may lead to increased VAT (Bjorntorp, 2001). For example, in response to stress, secretion of adrenocorticotrophic hormone (ACTH) has been found higher among men compared to women, although the adrenal cortex still produced the same level of cortisol as women (Roelfsema et al., 1993). This suggests greater sensitivity of the adrenal cortex to ACTH-induced cortisol secretion among women, which may lead to gain in VAT. In contrast, other studies have reported higher cortisol responses in men compared to women after exposure to acute real-life psychological stress (Frankenhaeuser et al., 1978; Earle et al., 1999), which might lead to greater VAT in men. Alternatively, the greater VAT (and, thus, accompanying low-grade inflammation) among men compared to women may lead to an interaction between sex and VAT resulting in more severe depressive symptoms among men (Demerath et al., 2007).

A few studies examining the depressive symptoms-VAT association have investigated differences by race. As previously mentioned, Vogelzangs et al. (2008) found significant interaction by race (White vs. Black) among women in the association between baseline EDS and change in VAT, specifically, a positive association among White women and a negative association among Black women. The reverse relationship (VAT leading to EDS) did not vary by race (Vogelzangs et al., 2010).

Minorities may experience greater psychological stress (e.g. due to discrimination, immigration, economic burden) compared to Whites (Logan and Barksdale, 2008), which may increase their risk for depression and VAT accumulation. Further, the stigmatization of depression, under-diagnosis and inadequate depression treatment are found more consistently among ethnic minorities than Whites (Strickland et al., 1997; Georg Hsu et al., 2008; Lin et al., 2011), which may lead to poorly controlled depression, hypercortisolism, and an increase in VAT.

Some antidepressants are associated with weight change (Sussman et al., 2001; Serretti and Mandelli, 2010). For example, certain Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. escitalopram, citalopram) have been associated with weight loss, whereas tricyclic antidepressants (e.g. amitriptyline, doxepin) have been found to induce weight gain (Serretti and Mandelli, 2010). Moreover, other antidepressants (e.g. trimipramine, paroxetine) have been shown to have both effects on weight (National Institute of Health, 2007; Serretti and Mandelli, 2010). Most studies on the association between depressive symptoms and VAT have primarily used scales for depressive symptoms (Lee et al., 2005; Weber-Hamann et al., 2006; Everson-Rose et al., 2009). However, the effects of antidepressant use in this relationship as a covariate or as part of the definition of EDS may be of particular importance as excluding antidepressant use may misclassify once severely depressed individuals who were treated and controlled at the time of assessment, but whose prior depression has already influenced VAT, as not having EDS. As antidepressant use has also been more common among Whites than ethnic minorities (Gonzalez et al., 2008, 2009, 2010), exclusion of medication use to define EDS may also misclassify a large portion of this cohort. Another consideration, however, is that anti-depressants can be prescribed for indications other than depression, resulting in another source of misclassification. Given the potential effect of antidepressants on weight and their use in non-depressive disorders, it is important to consider EDS definitions with and without anti-depressant use in assessing the depressive symptoms-VAT relationship.

In this study, we evaluated the cross-sectional association between depressive symptoms and VAT, and whether this relationship varies by race/ethnicity and/or sex.

2. Methods

2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center, community-based cohort study on the prevalence, correlates and progression of subclinical cardiovascular disease. The first examination (visit) took place in 2000 through 2002, when 6814 Whites, Chinese, Blacks and Hispanics Americans ages 45–84 years and free of known cardiovascular disease were examined at six US study sites: Baltimore, MD, Chicago, IL, Forsyth County, NC, Los Angeles, CA, New York, NY, and St. Paul, MN. Visit 1 occurred in 2000–2002, visit 2 in 2002–2004 and visit 3 in 2004–2005. Two other subsequent visits followed at the time of this report. The study was approved by the institutional review boards of each institution, and written informed consent was completed by each participant. The study design and objectives have been previously published (Bild et al., 2002).

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed during visit 3 using the Center for Epidemiologic Studies Depression (CES-D) Scale, a 20-item questionnaire developed to assess past week's depressive symptoms among community populations (Radloff, 1977), administered in English, Spanish, Cantonese, and Mandarin. Participants were asked to rate each item on a scale from 0 to 3 (range of total scores = 0–60). Although the CES-D is not an assessment of clinical depression, a CES-D score ≥ 16 has been found to be consistent with at least mild-to-

moderate depression or dysthymia (Beekman et al., 1997). Using this cut-off, sensitivity and specificity for major depression in the past year had been reported as 70.6% and 88%, respectively (Beekman et al., 1997). The internal consistency of CES-D has ranged between a Cronbach's alpha of 0.84 and 0.93 (Radloff and Locke, 2000) and has been found comparable in European, African, Mexican and Chinese-American groups (Radloff, 1977; Roberts, 1980; Cheung and Bagley, 1998). The CES-D has been used widely in cross-cultural epidemiological studies conducted with validated Spanish (Aneshensel et al., 1983) and Chinese versions (Cheung and Bagley, 1998).

For reasons previously discussed, we defined EDS as a CES-D cut-off of 16 and/or the use of antidepressants assessed at visit 3. We also performed sensitivity analyses comparing the results produced using different definitions of EDS, as follows: (1) CES-D ≥ 16 only; (2) CES-D ≥ 21 only; and (3) CES-D ≥ 21 and/or the use of antidepressants. A CES-D cut-off of 21 has been considered as a clinical cut-point to indicate probable major depression (Zich et al., 1990). Analyses that used solely a CES-D cut-off to define EDS were adjusted for antidepressant use. Assessment of depressive symptoms as a continuous variable was also evaluated.

For the baseline and follow-up visits, participants were requested to bring containers of medications, including anti-depressants, which were used two weeks prior to the visit. The interviewers transcribed the name of each medication, its strength and, for prescription, the frequency of administration, from the containers. The condition for which anti-depressants were prescribed was not described. Medication labeled as antidepressants included monoamine oxidase inhibitors, SSRIs and tricyclic antidepressants.

2.3. Assessment of visceral adipose tissue

During visits 2 or 3, abdominal body composition using computed tomography (CT) scans was determined in 1944 participants enrolled in the MESA Body Composition, Inflammation and Cardiovascular Ancillary Study. Three CT equipment were utilized to obtain CT visceral fat measurements: Imatron C-150 electron-beam (NY, CA, IL), Siemens S4+ Volume Zoom (MN), and General Electric Hi Speed LX (NC) scanners. Imatron C 150 (GE Medical Systems, Milwaukee, WI) settings will be continuous volume scanning, collimation of 3-mm, 400 ms, slice thickness of 6 mm, reconstruction using 25 6-mm slices with a 35-cm field of view, and normal kernel. Siemens S4+ Volume Zoom scanners (Siemens, Erlanger, Germany) were set at spiral mode, 4 mm $\times$ 2.5 mm collimation, slice thickness of 5 mm, 120 kV, 180 mAs, table speed 3 cm/sec and pitch 6. The General Electric HiSpeed LX scanners (GE Medical Systems, Milwaukee, WI) were set at helical mode, 120 kVp, 250 mAs, 800 ms, 4 mm $\times$ 2.5 mm collimation, and a standard reconstruction kernel. All images were reconstructed using a 50 cm field of view. Electron beam CT and helical scanners operated with a constant pitch. From these scans, six selected slices from the L2–L5 vertebral spaces (i.e. two at L2–L3, two at L3–L4, and two at L4–L5) were obtained for measurement of VAT (in cm²). Using the Medical Imaging Processing Analysis and Visualization software (MIPAV version 4.1.2), two trained analysts evaluated each CT scan independently at a centralized reading center (UCSD, La Jolla, CA). Disagreements were adjudicated by the two readers and a study coordinator. Intraclass

correlations for the different measures of body composition ranged from 0.92 to 0.99. The Hounsfield Unit range used to classify tissue as fat was: -190 fat pixel -30 . The amount of VAT was defined as the sum of visceral fat in the six evaluated slices. To assess the proximal relationship between depressive symptoms and VAT, we limited analyses to visit 3 scans.

2.4. Covariates

Using standard protocols as previously described (Bild et al., 2002), covariates included socio-demographics (age, race/ethnicity, sex, marital status, study site, education, income), use of antidepressants, inflammatory markers (IL-6, CRP), health behaviors (pack-years of smoking, number of alcohol drinks consumed, total intentional exercise), comorbidity (type 2 diabetes, cancer, hypertension) and BMI. IL-6 and CRP were measured using ultra-sensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN) and the BN II nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL), respectively (Golden et al., 2007). Total intentional exercise was determined using a 28-item Typical Week Physical Activity Survey (Bild et al., 2002). Physical activity was summarized as the metabolic equivalent task of minutes per week (met-min/week) spent in moderate/vigorous household, outdoor, sporting, conditioning and volunteer activities. Self-reported cancer included a doctor's diagnosis for prostate, breast, lung, colon, blood, non-melanoma skin cancer, or other cancer. Type 2 diabetes was defined by fasting plasma glucose ≥ 126 mg/dl and/or use of medications for diabetes (Genuth et al., 2003). Hypertension was defined by a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg or use of anti-hypertensive medications (Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure, 1997). Blood pressure was measured in a seated position three times, and the average of the last two measurements was used. Weight and height were measured using a balance beam scale and a stadiometer, respectively, with participants wearing light clothing. BMI was calculated as weight (kg) per height squared (m^2).

When available and when sample size was not compromised, covariate values were obtained at the time of depressive symptoms and VAT assessment (i.e. visit 3): age, physical activity, and antidepressant use. Other covariates were evaluated at the baseline visit.

2.5. Statistical analyses

There were 1944 individuals from whom abdominal body composition was determined. For the current analysis, participants were excluded for the following reasons: participants with visit 2 VAT data ($n = 768$), no VAT data at visit 3 ($n = 35$), missing CES-D values ($n = 14$), missing data on anti-depressant use ($n = 25$), incomplete covariate values ($n = 82$) and utilizing weight reduction pills ($n = 3$). As such, a total of 1017 participants was included. Compared to study participants, individuals with missing VAT values had greater BMI and waist circumference and were more likely to be overweight, which may be reflective of scanner limitations. They were also more likely to be male, less likely to be married, have greater levels of inflammatory markers, and are more likely to report hypertension.

Linear regression was used with VAT as the dependent variable and depressive symptoms status as the primary independent variable adjusting for a series of covariates. To account for varying visceral compartment size among individuals, all models were adjusted for BMI and age. Adjustment by these variables was done in Model 1. Socio-demographics were added in Model 2, and the fully adjusted model (Model 3) also included inflammatory markers, health behaviors and comorbidities. Covariates were chosen based on biological plausibility and those that were found to confound or potentially mediate the association between depressive symptoms and VAT from prior studies.

Race/ethnicity and sex were assessed as potential modifiers. Three dummy variables were created for race/ethnicity, with the White population as the referent group, each of which was multiplied by depressive symptoms status to create three 1st order interaction terms for race/ethnicity. Wald tests were used to evaluate the combination of these terms to assess additive interaction by race/ethnicity comparing Whites to ethnic minorities. As an exploratory analysis, each interaction term was also evaluated comparing Whites to each minority group. Assessment of interaction by sex also used a 1st order interaction term, and both of these analyses were modeled using fully adjusted models

All analyses were completed using STATA (StataCorp. 2012. *Stata Statistical Software: Release 12*. College Station, TX). *P*-values were considered significant at a 2-sided *p*-value <0.05.

3. Results

Of those who were categorized as having EDS ($n = 191$, 18.8%), 48.7% ($n = 93$) were classified based primarily on CES-D ≥ 16 (i.e. no antidepressant use); 13.6% ($n = 26$) had both CES-D ≥ 16 and antidepressant use; and 37.7% ($n = 72$) were classified based solely on antidepressant use (i.e. CES-D < 16).

Table 1 illustrates the population characteristics by sex and EDS status. Among women, 24.9% had EDS and 50.4% of those with EDS utilized antidepressants. In this cohort, compared to those without EDS, those with EDS were younger, more likely to be White or Hispanic, and had negligibly greater BMI. Among men, 12.6% had EDS of which 53.1% utilized antidepressants. Men with EDS were more likely to be single, had negligibly greater BMI and had greater VAT compared to their counterparts. Compared to men, women had significantly higher CES-D scores ($p < 0.0001$) and were more likely to use antidepressants ($p = 0.002$).

Among the entire cohort, the presence of EDS was not significantly associated with VAT; however significant modification by sex was observed ($p = 0.007$, Table 2). While a null relationship was found among women, among men, EDS was related with greater VAT (a 94.7 cm² difference in the fully adjusted model, CI = 10.5, 178.9). The findings were similar in significance, and stronger in magnitude, when EDS were defined as a CES-D ≥ 21 and/or the use of antidepressants. Using solely depressive symptomatology (i.e. CES-D score) to define EDS (with adjustment for antidepressant use) also produced similar trends when stratified by sex; however, the interaction *p*-value was not significant (see supplemental table).

Supplementary Table 1 related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psyneuen.2014.05.004>.

There was no significant interaction between EDS and race/ethnicity for visceral fat; however, statistical power may be limited.

Associations between continuous CES-D and VAT were not statistically significant.

4. Discussion

Overall, we found the association between depressive symptoms and VAT to vary by sex, but not by race/ethnicity. Specifically, EDS was significantly related to more VAT among men, but not among women, independent of socio-demographic factors, inflammatory markers, health behaviors, comorbidity and BMI.

Our findings for VAT are distinct from results of previous studies (Lee et al., 2005; Weber-Hamann et al., 2006; Everson-Rose et al., 2009; Murabito et al., 2013). Everson-Rose et al. (2009) and Murabito et al. (2013) reported significantly greater VAT associated with EDS among women. Our results for women were not significant. The study by Murabito et al. (2013) also did not present significant results for men as we found in our study. However, the men in the investigation by Murabito et al. (2013) were about 10 years younger and may be more physically active due to less age-related limitations. This may reduce their VAT and potentially attenuate depressive symptoms. In the investigation by Everson-Rose et al. (2009) showing a significant positive association among women, the participants were younger (age range 42–52 years) and pre- and peri-menopausal, in contrast to the women in our cohort, many of whom may be post-menopausal given an average age of 63.5 years. The study by Weber-Hamann et al. (2006) showed a positive relationship; however, treatment of all depressed study participants with antidepressants during follow-up may have resulted in increased VAT which was not considered in the study. When depressive symptoms were modeled as a continuous variable, our null results supported similar findings by Lee et al. (2005). This suggests a threshold effect by which health consequences of depressive symptoms only appear at high symptom levels. Further, although Vogelzangs et al. (2008) found baseline depression associated with a 5-year increase in VAT among men, they also showed this association among White women, but a negative relationship among Black women. Conversely, evaluating the association between VAT and subsequent depressive symptoms over 5 years, the same group found a positive significant association only among men, but not women (Vogelzangs et al., 2010). Because our data were cross-sectional, we could not explore these longitudinal associations.

Antidepressants may influence weight with the direction dependent on the type prescribed (Serretti and Mandelli, 2010). The trivial difference in estimate between models with and without adjustment for antidepressant use (in our analyses defining EDS using solely CES-D scores) suggests that its influence is negligible in our study population. The major change in baseline characteristics when antidepressant use was included in the definition for EDS was the 15.3% increase in White participants with elevated depressive symptomatology, 35.8% of whom were males. With this inclusion, Whites had the highest prevalence of EDS compared to other race/ethnicities. Although this may reflect better access to treatment for

depression among Whites versus ethnic minorities, inclusion of antidepressant use in the EDS definition may also represent controlled depression which may have previously lead to increased VAT. Men have been shown less likely to seek treatment for depression than women (Addis and Mahalik, 2003), and the relatively lower prevalence of antidepressant use among men in this study may be indicative of this behavior. Men who are on antidepressants may be more severe cases, which have stronger associations with VAT. Further, a negative view of how others perceive depression has been shown to be stronger among men compared to women (Griffiths et al., 2008), and may reinforce social desirability bias in this cohort. This may, in turn, lead to relatively lower reporting of depressive symptoms by men when using a screening tool as seen in our study.

Depression among men may be manifested through increased consumption of alcohol (Kessler et al., 1994) which may lead to greater adiposity, possibly explaining our results. Alcohol abuse may mask depression, as well as elicit or propagate depressive symptomatology. Although we adjusted for the number of alcohol drinks consumed, residual confounding may remain as this covariate was assessed at baseline. The accumulation of escalated and recurrent stress may lead to greater dysfunction of the HPA axis and hypercortisolism, and, subsequently, an increase in VAT (Bjorntorp, 2001). They may differ by sex, although the mechanism remains unclear. Kalynchuk et al. (2004) found sex differences in a preclinical study in response to repeated exposure to the stress hormone corticosterone, with stronger association in males than females. This is further supported by a randomized clinical trial on the differential influence of harassment on salivary cortisol stress reactivity in which men had twice the response as women (Earle et al., 1999). Frankenhaeuser et al. (1978) also found higher cortisol and a greater increase in psychoneuroendocrine response to stress among males compared to females. Thus, in addition to higher levels of cortisol, an elevated neuroendocrine stress reaction may lead to greater VAT among males. Leptin resistance has been proposed as another mechanism linking obesity to depressive symptoms. Using the Health, Aging and Body Composition study, Milaneschi et al. (2012) found a significant positive association between leptin and depressive symptoms in men with relatively high compared to low VAT, but no such association or interaction among women. The coexistence of high VAT and leptin may be necessary for the development of EDS in men, but less important in women with high VAT, in whom other biological (Cushman et al., 1999) or psychosocial (Maciejewski et al., 2001; Kendler et al., 2005) factors may better explain the association between VAT and subsequent changes in depressive symptoms.

One of the limitations of our study is its cross-sectional design, which did not allow assessment of temporality. Another limitation is our inability to determine the clinical relevance of the difference in VAT that we observed. Additionally, the use of CES-D to assess depressive symptoms is not equivalent to a diagnosis of clinical depression. The CES-D, however, has been validated in the literature as having good reliability and validity (Radloff, 1977; Haringsma et al., 2004); its reliability is comparable in European-American, African-American, Mexican- and Chinese-American groups (Roberts, 1980; Golding and Burnam, 1990; Li and Hicks, 2010). Including anti-depressant medication use in the definition of EDS may have resulted in misclassification, as antidepressants are not limited to treatment of depression, biasing our results toward the null. Therefore, our results are

likely a conservative estimate of the EDS-VAT association. The association we found in this study may also be driven by the relationship between depressive symptoms and use of drugs other than antidepressants that we did not capture (e.g. atypical antipsychotics, mood stabilizers) many of which have serious metabolic side effects such as weight change. By including several covariates in our analyses, about 25% of the sample was lost due to missing values. However, the significant differences in a number of highly relevant covariates were in the direction that would likely strengthen the association we found. Thus, our current analysis is conservative. Further, as a number of covariates were assessed at baseline rather than visit 3 to correspond with measured depressive symptoms and VAT, residual confounding by these variables may remain.

An important strength of our study is that MESA collected data on several covariates such as socio-demographics, anti-depressant use, inflammatory markers, health behaviors, comorbidities and BMI, allowing us to explore several mechanisms and account for potential confounding/mediation. We also measured VAT specifically using CT scans, considered a gold standard measure. Further, MESA is unique in including four race/ethnic groups: White, Chinese, Black and Hispanic, which might be more inclusive of the racial/ethnic profile in the US, thus improving the study results' external validity.

Our study provides support for the association between EDS and greater VAT among men, but not among women. Significant modification by sex was found when antidepressant use was included in the definition of EDS, possibly capturing individuals with once severe but currently controlled depressive symptomatology. Prior to successful management, the relationship between depressive symptoms and VAT may have been already established. This was particularly noted among men in whom greater disease severity compared to women may have previously developed due to less treatment-seeking behavior. Future studies assessing the relationship between depressive symptoms and VAT should be longitudinal so as to attempt delineating the temporal relationship between these variables. In addition, studies are needed to determine the clinical relevance of the difference in VAT we observed in predicting adverse health outcomes. Further, assessments of hormonal patterns (Lovejoy, 1998; Piccinelli and Wilkinson, 2000; Altemus, 2006), as well as HPA activity, may provide insight into the mechanism differentiating this association in men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline population characteristics by sex and elevated depressive symptoms status (EDS^a, N = 1017).

	Women (n = 511)		Men (n = 506)		p-Value ^b	p-Value ^b
	No EDS (n = 384, 75.1%)	EDS (n = 127, 24.9%)	No EDS (n = 442, 87.4%)	EDS (n = 64, 12.6%)		
CES-D						
Mean	5.5 (0.2)	16.2 (0.8)	4.9 (0.2)	16.4 (1.4)	<0.0001 [*]	<0.0001 [*]
Use of antidepressants						
Yes (%)	NA	50.4 (n = 64)	NA	53.1 (n = 34)	NA	NA
Demographics						
Age, in years (mean)	65.9 (0.4)	63.8 (0.8)	63.4 (0.5)	61.7 (1.1)	0.017 [*]	0.184
Race (%)					0.001 [*]	0.186
White	46.6 (n = 179)	52.0 (n = 66)	49.6 (n = 219)	56.3 (n = 36)		
Chinese	11.5 (n = 44)	7.1 (n = 9)	15.4 (n = 68)	9.4 (n = 6)		
Blacks	21.9 (n = 84)	8.7 (n = 11)	14.7 (n = 65)	7.8 (n = 5)		
Hispanics	20.1 (n = 77)	32.3 (n = 41)	20.4 (n = 90)	26.6 (n = 17)		
Marital status (%)					0.819	0.039 [*]
Married	57.3 (n = 220)	55.1 (n = 70)	79.0 (n = 349)	67.2 (n = 43)		
Widowed/divorced/separated	34.9 (n = 134)	35.4 (n = 45)	14.9 (n = 66)	18.8 (n = 12)		
Single	7.8 (n = 30)	9.5 (n = 12)	6.1 (n = 27)	14.1 (n = 9)		
Education (%)					0.065	0.886
Less than high school	14.8 (n = 57)	23.6 (n = 30)	14.0 (n = 62)	14.1 (n = 9)		
High school graduate	19.8 (n = 76)	19.7 (n = 25)	9.1 (n = 40)	10.9 (n = 7)		
College or greater	65.4 (n = 251)	56.7 (n = 72)	76.9 (n = 340)	75.0 (n = 48)		
Income (%)					0.185	0.207
<\$25,000	35.1 (n = 116)	39.1 (n = 45)	28.4 (n = 91)	35.9 (n = 19)		
\$25,000 and <\$50,000	36.6 (n = 121)	32.2 (n = 37)	33.0 (n = 106)	32.1 (n = 17)		
\$50,000 and <\$75,000	16.9 (n = 56)	22.6 (n = 26)	27.1 (n = 87)	15.1 (n = 8)		
\$75,000	11.5 (n = 38)	6.1 (n = 7)	11.5 (n = 37)	17.0 (n = 9)		
Inflammatory markers						
Median IL-6 (pg/mL) ^c	1.1 (0.8, 1.8)	1.3 (0.8, 1.9)	1.0 (0.7, 1.6)	0.9 (0.7, 1.5)	0.256	0.560

	Women (n = 511)		Men (n = 506)		p-Value ^b	p-Value ^b
	No EDS (n = 384, 75.1%)	EDS (n = 127, 24.9%)	No EDS (n = 442, 87.4%)	EDS (n = 64, 12.6%)		
Median CRP (mg/L) ^c	2.6 (1.1, 5.5)	2.8 (0.9, 5.8)	1.3 (0.6, 2.6)	1.3 (0.8, 2.8)	0.943	0.384
Health Behavior						
Number of alcohol consumption per week	2.2 (0.2)	1.9 (0.3)	5.8 (0.5)	6.8 (1.2)	0.500	0.449
Pack-years of smoking	8.8 (0.9)	9.1 (1.4)	14.9 (1.8)	15.7 (2.8)	0.887	0.880
Median exercise (met-min/wk) ^c	840 (210, 1779)	630 (0, 1800)	1050 (368, 2213)	840 (0, 2231)	0.212	0.191
Comorbidities (% Yes)						
Diabetes	8.6 (n = 33)	11.0 (n = 14)	9.3 (n = 41)	12.5 (n = 8)	0.411	0.415
Cancer	8.6 (n = 33)	7.9 (n = 10)	7.7 (n = 34)	4.7 (n = 3)	0.800	0.388
Hypertension	44.5 (n = 171)	52.0 (n = 66)	38.7 (n = 171)	39.1 (n = 25)	0.145	0.957
Anthropometry						
Height, in m (mean)	160.1 (0.4)	160.0 (0.7)	173.5 (0.4)	172.7 (1.0)	0.937	0.429
BMI, in kg/m ² (mean)	28.0 (0.3)	29.2 (0.6)	27.5 (0.2)	28.7 (0.6)	0.049*	0.024*
Overweight/obese (%) ^d	65.9 (n = 253)	70.9 (n = 90)	71.3 (n = 315)	78.1 (n = 50)	0.300	0.253
Visceral fat mass, in cm ² (mean)	767.6 (20.6)	820.5 (34.3)	1150.0 (23.5)	1334.4 (74.4)	0.197	0.007*

^aElevated depressive symptoms (EDS): CES-D 16 and/or antidepressant use; Of those who were classified as having EDS, 9.1% (n = 93) participants were classified based solely on CES-D 16 (i.e. no antidepressant use); 2.5% (n = 26) had both CES-D 16 and antidepressant use; and 13.1% (n = 72) were classified based solely on antidepressant use (i.e. CES-D < 16).

^bTo determine p-values, t-tests and χ^2 tests were used for continuous and categorical variables, respectively. For non-normally distributed variables, Wilcoxon rank-sum test was used.

^cSummary statistic represents median (interquartile range).

^dOverweight/obese: waist circumference: >88 cm (women) and >102 cm (men); BMI 25 kg/m².

* Significant p-value < 0.05.

Table 2

Difference in visceral fat (cm²) (95% confidence interval) between those with and without elevated depressive symptoms (CES-D 16 and/or antidepressant use), all participants and stratified by sex^a (*N* = 1017).

Model	All (<i>N</i> = 1017) ^{b,c}	Sex	
		Women (<i>n</i> = 511) ^b	Men (<i>n</i> = 506) ^b
M1: BMI, age	−48.3 (−112.1, 15.4)	−2.5 (−70.2, 65.1)	122.5 (34.3, 210.7)*
	Adj. <i>R</i> ² = 0.35	Adj. <i>R</i> ² = 0.55	
M2: M1 + demographics ^d	6.8 (−46.0, 59.6)	−46.0 (−112.0, 19.9)	96.9 (11.1, 182.6)*
	Adj. <i>R</i> ² = 0.59	Adj. <i>R</i> ² = 0.59	
M3: M2 + inflammatory markers ^d + health behaviors ^d + co-morbidities ^d	−13.1 (−83.7, 57.4)	−51.3 (−116.4, 13.8)	94.7 (10.5, 178.9)*
	Adj. <i>R</i> ² = 0.60	Adj. <i>R</i> ² = 0.60	

^a Interaction *p*-value: sex = 0.007 (fully adjusted); models were assessed using linear regression.

^b All participants: mean visceral adipose tissue = 976.1 cm² (range = 97.0–3169.2 cm²); women: mean = 780.8 cm² (range = 746.0–815.6 cm²); men: mean = 1173.3 cm² (1128.7–1.217.9 cm²).

^c Adjusted for gender.

^d Demographics = race/ethnicity, marital status, income, education, study site; Inflammatory Markers = Interleukin-6, C-reactive protein; Health Behaviors = pack-years of smoking, number of alcohol drinks consumed per week, total intentional exercise; Co-morbidities = cancer, hypertension, diabetes.

* Significant main effects *p*-value < 0.05.